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An overview of Stress in cellular and molecular levels and the importance of studying responses to stresses in biology

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Abstract: Stress in psychology and biology is defined as any environmental or physical pressure that elicits a response from an organism. In most cases, stress promotes survival because it forces organisms to adapt rapidly for changing environmental or internal conditions. Whether cells encounter to stresses, responses highly could be different pertain on their environments, duration, type of stresses as well as kind of cell. Living organisms can respond to stresses by various mechanisms. There are often interactions between disparate responses that finally determine the destiny of the cell under stress from the activation of survival pathways to initiation of eliminating damaged cells. The most crucial roles in responding to stress are played by Signal Transduction Systems which are involved in many cellular processes as well as regulating and maintaining internal micro environmental and homeostasis, differentiation, proliferation or finally the cell death. These processes are highly conserved in organisms during evolution. Mammalian cell mechanisms respond to different stresses include; the DNA damage, the unfolded protein, mitochondrial signaling stress, proliferation or elimination of damaged cells responses. Plant and microorganisms have three levels of defending against stresses, Plasma membrane and cell wall (1), cytosolic and molecular adaptability such as salt-in, salt-out and Compatible solutes strategies (2) and finally gene regulation (3). New evidence recently shows that interaction through biotic and abiotic stresses causes to positive effects on gaining more tolerance and performance in plants under stressed environment with increasing threshold to stressors by crosstalk mechanism which lead to cross-tolerance and enhancement of a plant's resistance against pathogens. In this review we are going to discuss the stress in three aspects; Basic principles of stress (1), stress response fundamental mechanisms(2) and Relation of stress response and defense mechanisms in three domains of lives (3) at the end using stress Responses to ameliorate diseases has been explained.
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Introduction:

Every organism is shaped by its environment. From tiny bacteria to elephant or a wale with weighing 200 tons and fungi that extensions for hundreds of hectares underground, the diversity and scope of life on Earth is flaring in its strategies to proliferation and reproduction process. Organisms inhabit nearly every environment on the Earth, from hot and deep valleys on floor of oceans to the icy areas of the Arctic. Each environment offers both resources and constraints (stressors) that shape the appearance and performance of the organisms (5, 6, and 7).

Stress, in psychology and biology is environmental or physical pressure that elicits a response from an organism (12, 3), in other words, any factor that seriously threatens homeostasis in Oregon (74). In most cases, stress promotes survival because it forces organisms for adapting and/or changing environmental or internal conditions rapidly (12, 3). The threat or stimulus is described as a "stressor" and a response to a tension is called "stress response"(74).

Multi-omics studies and integrated approaches comprising genomics, transcriptomics, proteomics, metabolomics on organism under stressed situation can help us to have better comprehension of organism responses to internal or external stressors and their relationships and interactions, these studies will lead to generate multi-layered information that can answer what is happening in real-time within the cells under stress condition. In this article we are going to discuss on stress in three aspects; (1), Basic molecular principles of stress responses (2) and Relation of stress response and defense mechanisms three domains of lives (3).

1. Basic principles of stress

As far as physiologists are concerned, stress is a well-known factor that has driven evolution and development of organism ecosystems since life began. An organism's ability to tolerate stress is a major key to survival in environments that change rapidly; the organism must have Mechanisms for sensing and responding to alterations in their surroundings. Organisms constantly adjust to these changes by adapting their internal chemistry (homeostasis) or their location in the environment (8 and 3).

In spite of advantages of stress, in biotic communities, stresses may cause loss of biomass, impoverishment of species, or degradation in tough environmental conditions. Stress usually becomes an important agent in decreasing organism potential when it exceeds a threshold of biological tolerance. It may then constrain or restrict ecosystem development (8, 9). Stresses can be induced by the surrounding environment or come from biological pathogens that lead to disease or/and interaction between environmental and biological elements which lead to damage in all of the kingdoms of life. (19).

Biodiversity is restricted by many factors that one of them is stress. Environment with highly stressful condition tends to have low biodiversity though the biodiversity can be much higher if stress does not have a strong presence in the area (12, 13).

Type of stresses:

Generally all of organisms depend on environments which surrounding them have been affecting by two types of stress which are called abiotic and biotic stresses (12, 13). They are causing the most major effects on organisms which important stresses in biology have been shown by tablet 1.

Most organisms live in ever-changing environments, the ability of cells to receive and act on signals from beyond the plasma membrane is fundamental aspect of life. In uncertain environments, organisms not only react to signals, but also use molecular processes to make guesses about the future (17 and 16).

2. Stress response fundamental mechanisms

Cells perceive permanent information as signals from environment by membrane proteins are named receptors. These signals include pH, osmotic strength, the availability or Shortage of food, oxygen, light and biological pathogens which can create appropriate responses in the cell, such as move toward food, escape from toxic substances or the formation of dormant spores in a nutrient-depleted environment (51). In multi-cellular organisms, cells with various functions exchange wide varieties of signals like Animal cells that exchange information related to concentrations of ions, glucose or existence of hormones in extracellular fluids after that the proper interdependent metabolic activities taking place in different tissue cells in general or targeted one exclusively. Plant cells show reaction to different hormones or stimulators to variations in environmental stressors. In all of these examples, signals display information that is detected by particular receptors and transformed to intracellular chemical responses. All of this processes which converted of information into a chemical changes are called signal transductions and they are universal property of all living organisms in biology territory (17 and 16).

2.1 General Features of Signal Transduction

Biological functions such as responses to hormones and growth factors, the senses of sight, smell, and taste; the transmission of nerve signals; and control of the cell cycle. Often, the end result of a signaling pathway

is the phosphorylation of a few specific target-cell proteins, which changes their activities and thus the activities of the cell. Biological signaling pathways are essential mechanisms of signal transductions and adaptation of each living organism in wide range of organism activities.

Signal transductions are extremely specific and highly sensitive which is achieved by the punctual molecular complementary state between the signal and the receptor molecules (52). there are three factors that responsible for the extraordinary sensitivity of signal transduction: the high affinity of receptors for signal molecules (1), cooperative in the ligand and receptor interactions (often but not always) (2), amplification of the signal by enzyme cascades(3), there are 6 common component in every signal transduction, they have been illustrated by figure 1.

In figure 2 as an example has been shown the all components of signal transduction in the Sho1 branch which has key role in the high-osmolarity glycerol (HOG) pathway and will be discussed in this study further (21 and 22).

Signaling pathways consist mainly of formed chain proteins which are conserved and protected during evolution. In this process, proteins interact with each other in a particular sequence with the previous sequence. Generally, each organism possesses in common essential intracellular signaling mechanisms; in spite of some components are dominant and general; others have specific paths which produce unique result in each area of life (21 and 22). If discussed in general in territory of biology each organism has four types of signaling mechanisms (fig 1 and 2).

1 - G protein–coupled receptors (GPCR) that indirectly activate (through GTP binding proteins or G proteins) enzymes that generate intracellular second messengers.

2 - Receptor enzymes in the plasma membrane that have an enzymatic activity on the cytoplasmic side, triggered by ligand binding on the extracellular side. Receptors with tyrosine kinase activity, for example, catalyze the phosphorylation of Tyr residues in specific intracellular target proteins. The insulin receptor is one example.

3- Gated ion channels are one of the simplest signal transducers of the plasma membrane which open and close hence they are termed gated, they react to the binding of chemical ligands or changes in ionic transmembrane potential.

4 - Intracellular receptors (nucleus and cytosol) like androgen receptors that bind specific ligands to steroid hormones such as the estrogen and alter the rate at which specific genes are transcribed and translated into cellular proteins (fig 1) table 2 shows common types of cell receptors.

As illustrating in Figure 3, Extracellular signals may belong to various mineral or biochemical molecules, they can be short or distance, small or large and hydrophobic or hydrophilic molecules. Correspond to neurotransmitters, hormones (including local hormones), cytokines, growth factors, cell surface molecules and sensory stimulation molecules (21 and 22). In multi-cellular organisms, these signals are joined to receptors by means of 4 mechanisms: juxtacrine, autocrine, paracrine and endocrine. Signals may be freely present in the intercellular fluid or embedded in the extracellular matrix, and the response to the signal will depend on the existence of a specific receptor to the particular signal in the cell. (21, 22 and 75). In summary, cells require to participate of five subunits of intracellular signaling pathways simultaneously or approximately sequentially during the cell division and proliferation cycles (52) as it has been shown in Figure 3:

Stage 1 indicates that primary message releases as ligands then cells react to them as well as mammalian cells respond to hormones or other stressors. Bacteria, eukaryotic microorganisms, and vascular plants must also respond to a large number of external signals such as O2, nutrients, light, harmful chemicals, and so on (21 and 22).

Step 2 illustrates reception of signal; the intracellular components of the signal transducer are very particular to receptors, thus maintaining the specificity of the input signal within the cell (76).

In step 3, signal transduction pathways utilize a network of enzymes that act on each other to amplify the input signal, which produces a physiologically accurate and appropriate response by the cell. Signal transmission initiates to alter the behavior of proteins in the cascade form and actually turning them on or off like switches. One of the basic mechanisms for deformation resulting from the behavior of a protein is the addition or elimination of phosphate (77).

The ligands stimulate their own specific receptors, thereby inducing the production of a second messenger; there are Several small molecules which act as intracellular messengers also known as secondary messengers like cAMP, cGMP, nitric oxide, lipids and Ca2 ions that in turn activates or deactivates other enzymes, so the message transfer cascade can be continued (78). Each route may include more than 200 constituents in horizontal rows (upstream and downstream sequences) and vertical rows (different waterfalls or families), as this is particularly the case in MAPK routes. In addition, each signaling pathway subunits, directly or indirectly, is associated with other pathway subunits lead to the physiological effects of proliferation or cellular activities (21 and 22). It should

be noted that steps 4 and 5 of Figure 3 will be explained in the following sections:

2.2 Signaling mechanisms in Microorganisms and Plants

In prokaryotic and eukaryotic microorganisms, there are various sensory systems that enable them to respond appropriately to their changing environment. There are two component systems available in bacteria, a receptor His kinase that senses the signal thereupon auto phosphorylates a His residue, and then phosphorylates an Asp residue of the response regulator (2). Plants react to variety of environmental stimuli and apply hormones and other factors for regulating cellular and metabolic activities in their tissues. The plant genome encodes hundreds of signaling proteins, some of which have sequences very similar to their homologous samples in animals. The transducer molecules convey the information to the sensor molecules into the cell and the effective molecules. The first intermediates or final elements of specific signaling pathways (Step 4 in Fig. 1). Some effects on proteins (for example, transcription factors) may operate on single or multiple molecular targets and fulfill cellular processes such as exocytosis, phagocytosis, actin remodeling, activation of metabolic pathways, and gene expression (step 5 in Figure 1) (20).

3. Relation of stress response and defense mechanisms in three domains of lives

In this section we are going to discuss some common examples of perceive, transduction and response to stress in cellular and molecular level in three domain of life which called Archaea, Bacteria and Eukarya cells (2).

Animal (Eukaryotic Cell) cells response and defense to stress

In this way, sense organs are very sensitive to certain kinds of stimuli or stressors and deliver their information to surface of target which is celled specific ligands. One cell can have many different receptors on the surface or inside that receive signals and transmit them through of the cell parts at the same time. Briefly, all type of cells use specific intracellular signaling pathways to record incoming information then translate it to make different molecule interacts then produce a biological response to the signal (8, 21, 22 and 16).

3.1. Stress leads to cell death

Many stressors have been shown to induce cell death such as oxidative and ER stress, chemotherapeutic agents, irradiation and etc.

3.1.1 Programmed cell death or apoptosis

Apoptosis or cell death or based on the original definition by Kerr Wyllie and Currie in 1972 refers to autophagic cell death. It is a term which used to explain a specific type of cell death that is common to many aspects of physiological cell death. The morphology of Programmed cell death contains cell contraction and rounding, membrane blebbing, cytoskeletal and nuclear collapse as well as margination, condensation and fragmentation nuclei or chromatin. Also, in most cases the process of phagocytosis destroys cell fragments without the inflammatory response that is rapidly digested by phagocytosis by macrophages or neighboring cells without activating the immune response (29, 21 and 33). The process of the apoptosis is highly protected during evolution and executed a major physiological obligation in development, proliferation and aging of organisms (29, 21 and 22).
The morphology of cells undergoing apoptosis is completely different from the morphology of cells which associated with necrosis or phagocytosis, They are discussed below (32). Programmed cell death could be initiated by the extrinsic and intrinsic pathways. Extrinsic pathway is started by the participation of death ligands like the TNF – superfamily or apoptosis-induced ligands, TRAIL, tumor necrosis factor, etc. then ligand recognizes and bonds to its receptor, next a set of intracellular pathways are figure out to activate the initiator caspases. With transferring information into the cell intrinsic pathway is started by over expression of interleukin-1β-converting enzyme (later named caspase-1) has been demonstrated to be played a key role to compel programmed cell death in mammalian cells (33, 34 and 35), Caspases are a family of cysteine proteases that act as common death effectors molecules in various forms of apoptosis. They are synthesized as inactive pro-enzymes, after activating they various substrates are cleaved by them in the cytoplasm or nucleus which caused to many of the morphologic features of apoptotic cell death as well as poly-nucleosomal DNA fragmentation, loss of overall cell shape and nuclear shrinking, the process has been shown in figure 4 (16, 21, 33 and 22).

3.1.2 Autophagic Cell Death

Autophagy (self-eating) is important for maintaining cell homeostasis by destroying damaged intracellular organelles or abnormal proteins moreover involving in various kinds of Physiological and pathological phenomena. it is initiated as soon as cells are exposed to high stressful environmental conditions such as

infection to control proliferation, inhibition of the receptor tyrosine kinase/Akt/ mammalian target of rapamycin (mTOR), nutrient depletion, inhibition of proteasomal degradation, the accumulation of intracellular calcium, endoplasmic reticulum (ER) stress and death cell signaling, growth factor deprivation, ischemia/reperfusion (34 and 35).

This process has several steps that are determined by the vesicular decomposition, degradation of long-lived cytoplasmic proteins and organelles, for instance, mitochondria. This process is driven by applying of lysosomes and promotes which can survival during starvation periods, as the cellular energy level can thus be maintained. During autophagy double-membrane vesicle is called an autophagosome are generated. The discovery of autophagy related to find out of (Atg) genes in yeast firstly and subsequently in humans which has highly promoted of understanding the molecular mechanisms that are involved in the control of programmed cell death. The protein product of the tumor suppressor gene Beclin 1 (BECN1) is the mammalian homolog of Atg6 and shapes a multi-protein complex together with Vps34, a class III phosphatidylinositol 3-kinase, UVRAG (UV irradiation resistance-associated tumor suppressor gene), and a myristylated kinase (Vps15, or p150 in humans) . This complex is essential for constituting of the autophagosome. While this intricate structure is formed, Vps34 becomes activated and catalyzed the production of phosphatidylinositol-3-phosphateb which is necessary for vesicle nucleation (30 and 36). Reactive oxygen species (ROS) can cater a link between cellular stress signals and the induction of autophagy, when ROS copulation has been done, the result could be inactivated of the cysteine protease ATG4, which causes accumulation of the ATG8-phosphoethanolamine precursor that is needed for initiating of autophagosome complex. The link between autophagy and cell death is very intricate due to most cellular regulation levels autophagy acts as a stressor coping approach that inhibits cell death, but in some situations, this would be an alternative pathway to cell death. This complex interrelationship between autophagy and cell death emphasizes that responses to stressful conditionsare partly related at the molecular and cellular level.

Finally, it should be noted that important cellular molecular events under stress conditions that ultimately determine whether autophagy is a protective or destructive method have not yet been fully defined (16, 21 and 22).

3.1. 3 Necrosis

Necrosis, is a term which generally used by pathologists which related to any deaths by losing ionic balance control, absorption of water, swelling and cell lysis. Necrosis leads to cellular destruction, release of cellular constituents, stimulates of inflammatory reaction and ultimately instigation of immune cells against owned damaged cell**.** Necrosis in multicellular organisms has long been regarded as an uncontrolled, unregulated and random process of cell death and however, there is currently evidence that necrotic cell death is also regulated by a set of signaling pathways. Morphologically, necrosis is associated with increased the cell volume, organelle swelling and rupture of the plasma membrane Which eventually results are loss of internal content and cell death. Variety of signal transduction cascades have been defined that involved in the process of necrotic cell death. A lot of evidence has suggested that serine / threonine kinase RIP1 is one of the major mediators of necrotic cell death process, at least in death or Toll-like receptors. In addition, ROS and calcium are major mediators in the release of necrosis-activating signals and are involved in the development of various forms of necrosis, for example, stimulation of calcium concentration may cause DNA exposure to tumor necrosis factor (TNF) or ROS may be released into the cell by metabolic pathways.

As respects, the ER is the main major intracellular calcium storage, mitochondrial calcium has been determined to induced oxidative phosphorylation, to induced oxidative phosphorylation, Leadsto production of more generation of ROS. Cellular integrity is destroyed with damaging the organelles and macromolecules in the cytosol by both ROS and calcium which lead to cell death ultimately.

Moreover, Calpain-mediated calcium activation may disrupt and inactivate the caspases, Whereas, ROS can target the active site of caspase enzymes and disable them. There is evidence that many stimuli induce necrosis which can inhibit apoptotic machinery and do not let the cell enter the apoptotic process (16, 21 and 22).

3.1. 4 Ferroptosis

Ferroptosis was first introduced by Dixon as a novel cell death in 2012, as well as autophagy and apoptosis, the ferroptosis is an iron-dependent and r*eactive oxygen species (*ROS)-reliant cell death and accepted as an adaptive elimination way for the malignant cells. Also, this plays an critical role in reducing tumor growth by eliminating damaged cells that are deficient in nutrients by infection or environmental stress in the environment. It leads to major cytological changes, such as decreased or vanished mitochondria cristae, a ruptured outer mitochondrial membrane, condensed mitochondrial membrane (37). This process starts by an iron-dependent cumulation of lethal ROS in cells

that leads to induce erastin which inhibits the cellular uptake of cystine then blocking the intracellular antioxidant defense mechanism by limiting the production of intracellular glutathione (GSH), one of the major cellular antioxid.
ROS generation is iron-dependent as its accumulation and cell death can be suppressed by the iron chelator deferoxamine.The underlying molecular mechanisms remain poorly understood. the process of the Ferroptosis has been shows in figure briefly (figure 5) (37 and 38).

3.1.5 NETosis and ETosis

NETosis (NETs) in 2004 was defined as one kind of cell death. NETs is a new preventive cell approach and distinct from apoptosis as well as necrosis or Ferroptosis. This method protects the host cells against biological pathogens by methods such as the generation of neutrophil extracellular traps (NETs), phagocytosis, the formation of reactive oxygen species (ROS) and releases antimicrobial from vesicles (degranulation), this mechanism is used by Neutrophil. NETosis is a cell death associated with neutrophils, which is described by the formation of large network-like structures outside the cell (47 and 48).
Other cells, such as eosinophils, mast cells and macrophages, can have similarly result in cell death. Thus, the process was renamed to ETosis, meaning release of extracellular traps (ETs). The main cause of the formation of ETs is still unknown and their biological significance has been studied recently. During NETosis morphological changes will occur in the cell, including the nucleus and organelle membranes are disintegrated then granules and the composition of the nuclear or organelle components are released into the cytoplasm (49 and 47).
NETs can protect the cell from broad-ranging biological pathogens a as well as Gram-positive and negative bacteria, viruses, parasites, fungi. Moreover, Intracellular Intermediates can promote the NET generation including cytokines, hydrogen peroxide, chemokines, cholesterol and autoantibodies. Also, Pro-inflammatory factors like tumor necrosis factors (TNF) , interferon (IFN)-γ, IL-8, IL-17 could able to initiate NETosis (47).

3.2 The Heat Shock Response

The Heat Shock Response is One of the main survival activities of cells which was originally described as the biochemical response of cells to stressors like elevations in temperature of above normal condition. It has been recognized that many stimuli as well as oxidative stress, PH and heavy metals activate this response, too. One of the major outcomes of stress on the cell is the damage to proteins, including the accumulation of unfolded proteins (82).

In order to neutralize these phenomena, cells enhance the expression of chaperone proteins that assist in refolding of misfolded proteins and diminish protein aggregation. This mechanism is a temporary protection method and creates a condition known as heat tolerance, so the cells are exposed to various stress conditions, not only in the event of an increase in temperature, but also in other stresses such as oxidative stress, anticancer drugs, heavy metal, etc. become more resistant. (25, 19, 21 and 22). Most probably, Transcription and protein translation will generally stop when the response to heat shock begins due to reduction of the misfolded protein burden. Under this condition transcription factors that boost expression of a proper subset of protective genes are selectively activated which called heat shock factors (HSF) (25, 19, 21 and 22).When the cell is under stress likeoxidative stress, heavy metals and high temperatures, this conditions leads to accumulation of unfolded proteins which are activated HSF1 which in turn induce Hsp27 and Hsp70. Hsps are one type of inhibitors of cell death processes that promotes survival. Hsp27 and 70 are also interacted with other proteins that adjust the ability of cell survival (25, 19, 21 and 22) (figure 6).

3.3 ER stress leads to the unfolded protein response.

Proteinsin the Endoplasmic reticulummay be modified by posttranslational processing as well as glycosylation, disulfide bond formation, correct folding, and oligomerization. This process leads to produce mature proteins which have more effective structureto do cell goals or secrete out. For this purpose, there are cellular essential mechanisms for monitoring the ER environment. The unfolded protein response (UPR) is defined as activating the set of pathways while the cell is under harmful conditions like perturbation of Ca2+ homeostasis, starvation, oxygen deprivation or proteins glycosylation blockage that caused accumulation of unfolded proteins in the ER which lead to ER stress. (17, 19, 21 and 22).
Meanwhile endoplasmic reticulum (ER) is under stress leads to activate three ER stress receptors which are named activating transcription factor 6 (ATF6), inositol-requiring enzyme 1 (Ire1) and PKR-like ER kinase (PERK), and In the Golgi apparatus specific proteolysis must be exploit out for activating ATF6, XBP1 is of the ATF6 target genes. Ire1 catalyzes the alternative splicing of XBP1 mRNA that leads to express of the active XBP1 transcription factor. The three arms of the UPR inhibit protein translation, compel chaperone expression and boost ER-associated protein degradative pathways (17, 19, 21 and 22) (figure 6). (17, 19, 21 and 22) (figure 7).

3.4 Response to the Damaged DNA

DNA damage is a natural phenomenon such as metabolic or hydrolytic processes or under stressed conditions which are induced by exposure to stressors like irradiation, chemotherapeutic and genotoxic agent. These factors are categorized as physical, chemical or biological elements. They are leads to mutations or cancer by damaging cellular DNA (table 2) (83 and 84).

DNA damage response (DDR) is happen while DNA doubles (DSBs) or single (SSBs) strand break (DSBs) which mentioned as key lesions that induced the initiation of the DDR (5, 7and 85). Therefore, at times such as DNA replication and transcription where DSBs become SSBs, they would be highly susceptible to exposure to mutagenic conditions for instance chemical attack or nucleases. Under these conditions SSBs are preferentially generated, In other words, SSBs are also produced in specific DNA repair pathways (19 and 21). When DNA damage is detected, additional cleavage at the site of the DNA lesion is performed by ERCC1-XPF and XPG, which will eliminate the damage containing oligonucleotides, DNA repair solution to DNA damage is a process to certify cell Survival in the occurrence of sublethal damage. On the other hand, if the damage to DNA repair is too tolerable for the cell, damage to cellular stress will lead to the activation of effective mediating systems for cell death. Depending on the type of damage to the DNA, the cell initiates one of several DNA repair pathways, which ultimately ensures the accuracy of the DSBs. non-terminal ends and homologous recombination are two main ways to repair DSB. It must be mentioned that DNA repair in fact could be error free or disposed to error, Fundamental damage can be corrected by enzyme-catalyzed reversal or by alternatively via excision repair. The Mismatch repair process responsibility for eliminating of mismatched nucleotides and replacing with compatible nucleotides. New evidence shows that multi proteins have been detected which have specific duties in faultless and high-throughput DNA repair processes with maximum assurance(5, 7, 19, 21, 22 and39).

The repair pathways and their monitoring mechanisms create variety of complex networks that are directly linked to the cell cycle checkpoints as well as the mechanisms of cell death. A repair system that is susceptible to failure or complete failure to repair damaged DNA can not only lead to mutations but also initiate the process of the cell death pathway (41).

The MRE-11-Rad50-NBS1 (MRN) complex activates DSBs ataxia telangiectasia mutated (ATM) to indentify broken DNA also phosphorylates downstream substrates such as checkpoint kinase 2 (Chk2) that eventually phosphorylates p53.If the damage is high intense and cannot be maintained by the cell, pro-apoptotic p53 target genes are inducedsome complex such as Fas, Puma, Noxa and Bax, genes that boost rate of apoptosis (43). As an example, Serine/threonine-protein kinase ATR also named as ataxia telangiectasia and Rad3-related protein or FRAP-related protein1 in humans are enzyme that encoded by the ATR gene. They activate phosphorylates Chk1 and prevents cdc25c to mediated G2/M or alternatively cdc25a prohibitors to promote inhibition S-phase (21,22 and 42).

3. 5 Oxidative Response

A range of diverse reactive oxygen species (ROS) have been identified which can be defended by antioxidant defendant processes in the cell. In addition, there are various detoxifying enzymes as well as catalases, superoxide and dismutase (SOD), peroxidase and Glutathione (GSH). When antioxidant defense systems fail to protect the cell against oxidants, macromolecules in the cell can be damaged or destroyed by ROS in long-term and cell death program will be started. (9, 19) (Figure 8).

3.6 One example of relationships between stress and cancer

Nucleotides are released by a variety of cell types in response to multiple stress signals, such as injury, hypoxia and inflammatory condition, etc. Further, the nucleotides are hydrolyzed by the enzyme cascade as follows: ATP/ADP into AMP by NTPDases (CD39), AMP into adenosine by ecto-5′- nucleotidase (known as CD73), and adenosine into inosine by adenosine deaminase. Therefore, purinergic signaling is regulated by a series of cell surface-located ectonucleotidases. The balance between ATP/ADP, AMP, and adenosine is crucial in the control of tumor progression (95, 94 and 97).

The promise of cancer immunotherapy has not been accomplished into clinical successes in large part due to tumor-associated immune suppression that blocks effective antitumor immunity. During cancer progression, cells foster a tolerant microenvironment and activate a plethora of immunosuppressive mechanisms, which may act in concert to counter effective immune responses (94).

Purinergic signaling has emerged as an important player in cancer progression and is regulated by a series of nucleotidases. CD73 is a surface protein

encoded by the NT5E gene also is playing a crucial role in Purinergic signaling pathways (adenosinergic signaling). CD73 has both enzymatic and non-enzymatic functions in cells. Notably, increasing data have shown that CD73 is also a key regulator involved in the progression of cancer. Among the enzyme cascade, CD73, which catelyzes AMP breakdown to adenosine, has been found to be overexpressed in many types of cancer and promotes tumor progression. Also, it leads to the proliferation and migration, invasion in vitro, tumor angiogenesis and immune escape in vivo of cancer in human cells independent of its enzymatic activity however the non-enzymatic function of CD73 has not been well studied. Accumulating studies have shown that CD73 is a key regulatory molecule of cancer cells proliferation, migration and invasion in vitro, tumor angiogenesis, and tumor immune escape in vivo (95, 96 and 97).
Recent findings show a tumor-induced immunosuppressive mechanism, whereby tumor-derived CD73 functions as an ecto-enzyme to produce extracellular adenosine, which promotes tumor growth by limiting antitumor T-cell immunity via adenosine receptor signaling (98). Various factors and mechanisms are employed to regulate expression of CD73. With such important roles in cancer, CD73 has become an appealing therapy target. Recent findings show a tumor-induced immunosuppressive mechanism, whereby tumor-derived CD73 functions as an ecto-enzyme to produce extracellular adenosine, which promotes tumor growth by limiting antitumor T-cell immunity via adenosine receptor signaling. Various factors and mechanisms are employed to regulate expression of CD73(99). With such important roles in cancer, CD73 has become an appealing therapy target (100).

3.6.1 Molecular function

As studies have discovered the CD73 is a nucleotidase, catalyzes the hydrolysis of AMP into adenosine and phosphate. Notably, CD73-generated adenosine plays an important role in tumor immune escape. In addition to its enzymatic function, CD73 is also a signal and adhesive molecule that can regulate cell interaction with extracellular matrix (ECM) components, such as laminin and fibronectin, to mediate cancer invasive and metastatic properties [101 and 102]. Importantly, higher expression levels of CD73 are associated with tumor revascularization, invasiveness, and metastasis, and with shorter patient survival time in breast cancer (101). Moreover, recent studies confirm that CD73 promotes invasion, migration, and adhesion of human breast cancer cells (103 and 104). Upregulated expression of CD73 has been found in highly invasive human melanoma cell lines, but not in melanocytes or in primary tumor cells (105). Biological actions of CD73 (ecto-5′-NT) are mainly a consequence of the regulated enzymatic phosphohydrolytic activity on extracellular nucleotides. This ecto-enzymatic cascade in tandem with CD39 (ecto-ATPase) generates adenosine from ATP, which in turn activates adenosine receptors. In contrast to the intracellular generation of adenosine from cytosolic pools of adenine nucleotides catalyzed by cytosolic 5′-NT in the heart, production of extracellular adenosine by CD73 is likely the predominant means of adenosine generation in epithelial cells, despite depending tightly on the availability of extracellular AMP (106) (figure 9).

3 .7 Plant responds to multi stress at the same time (biotic and abiotic)

Abiotic stress such as cold, drought, salt, and heavy metals have largely harmful and in some cases lethal influences on organism's development, agricultural and human activities due to preparing food for world population which is growing to be approximately 9.8 billion in 205 (12).

It is expected that there will be many different sensors in the plant cell, although it should be noted that none have been approved for stresses such as cold, drought or salinity. All of these stresses have been indicated to initiate transient Ca2+ influx into the apoplast. In plants, cold, drought, and salt stresses stimulate the repletion of compatible antioxidants and osmolytes. A key step in the plant defense system is timely understanding of stress for having fast and efficient response to stimuli (54). After diagnosis, the plants' constitutive fundamental mechanisms lead to activate wrapped signaling cascades of defense which varies from one stress to another (55).
After the plant is exposed to biotic or abiotic stressed conditions specific ion channels, kinase cascades, reactive oxygen species (ROS), hormones and other components for responding to these stimulates are activated (15).
phytohormones like abscisic acid (ABA), salicylic acid (SA), jasmonic acid (JA), and ethylene (ET) stack in the cell and lead on to reprogramming of the genetic apparatus results for sufficient defense reactions and gain plant tolerance until minimize the biological damage which is caused by the stress(figure 9). Extensive studies have been attempted to simulate and model plant responses to multiple stresses, but under real conditions (in the field) a stress can severely affect the plant defense response or merge with another stress (57).

Therewith, plants under stress can be able to show disparate degrees of sensitivity pertain to the

environment condition, the developmental stage, severity of stress and plant species, etc. Various interactions can occur between stress-induced defenses which depend on a particular combination of stresses and even the degree of synchronization. Combination of stressors may have several effects on the plant, the second stress can lead to a greater damage. On the other hand, it is not fully understood whether concurrent stresses have relatively antagonistic, synergistic or additive effects, leading to more or less sensitivity to a particular type of stress (figure 7) (59).Evidence suggests that when plants are exposed to more than one stress, plants can respond differently and based on the plant's response to individual stresses, the response will not be predictable.

Salinity is one of the most important stresses among them because it has profound impacts on crop and food productions directly. The limiting factor in hypersaline environments are high concentration of NaCl and other salts. high temperatures, evaporation of water, UV radiation, low oxygen concentrations, unavailability of nutrients around the organism. It should be noted that studies have shown when there are several tensions, plants that are able to defend themselves against one of them can tolerate a variety of stresses (58).

This phenomenon is named cross-tolerance, representation that plants have a powerful regulatory system that lets them to adapt rapidly to a changing environment (79 and 80).

for instance, Resistance to both biotic and abiotic stress has been well studied that under stress like wounding others such as salt tolerance in tomato plants could be enhanced, as well as in a variety of crops through priming of defenses (86). This type of induced resistance could be attained by particular chemical stimuli as well as the resistance inducers BABA (beta-aminobutyric acid) or BTH (benzothiadiazole), genetic manipulation which lead to modifying of genes and proteins in plants or by previous contact with a special pathogen. Due to the intricacy of interactions in defense, in the present review, we aim to focus on the cross-tolerance between abiotic and biotic stress as a part of induced resistance for defense (1, 11, 12, 13, 14, 15 and) (figure 10).

3.8 Defense mechanisms in extremely halophilic microorganisms:

3. 8.1 Defend mechanism againts salinity by salt-in statergy:

Environment with high salinity is one of the main challenges to its microbial inhabitant. Microorganisms must cope to increased osmotic pressure and low water activity hence requiring peculiar adaptation mechanisms to salinity stress. (60)

one of the mechaniems which is use by microorganisems is salt-in statergy to attain to ion gradients through the cell membrane (accumulation of K , excretion of Na^+ , repletion of Cl^- versus the inside-negative membrane potential) needs to have energy dependent mechanisms (87). The essential energy is provided from the proton gradient upon the membrane, turned out by respiratory electron transport and/or the light-dependent proton pump bacteriorhodopsin. (61, 62 and 88). Na^+ is expelled from the cell by Na^+/H^+ antiporters ystems. K+ can be obtained by cells through K^+ channels passively in the membrane, as driven by the inside-negative membrane potential, but active, ATP-dependent K^+ transport systems are also present (89).

One of the most characteristic properties of the halophilic Archaea is highly acidic proteome approach in the case of low existence of in K+ media. In their proteomes, there are high excess of negatively charged amino acids, aspartic acid (Asp, D) and glutamic acid (Glu, E) instead of positive charge such lysine (Lys, K), arginine (Arg, R) and histidine (His, H). This property is shared by other 'salt-in' strategisese. Major alkali metal–cation transporters in halotolerant / halophilic microorganisms in tale 3 (4, 2 and 6).

3. 8.2 Compatible solutes strategy and Secondary metabolite biosynthesis

Mitogen-activated protein kinase (MAPK) pathways are accountable in yeast and animals for production of compatible osmolytes and antioxidants. These MAPK pathways are initiated by receptors/sensors as well as protein tyrosine kinases, G-protein–coupled receptors, and two-component histidine kinases. Amongst these receptor-type proteins, histidine kinases have been unambiguously detected in plants. (62).

Most bacteria and eukaryotic organisms use the strategy of ''compatible solutes'' accumulation for maintaining their intracellular concentrations of Na+ below the toxic levels for the cells. The nature of compatible solutes in the cytoplasm are in such a way that do not interfere with the normal activity of the enzymes and the cell also tries to keep the concentration of inorganic ions in the apoplast environment to a minimum.

Many compounds of compatible solutes has been identify as antibiotics or immune suppressants. They are used as medicine or for organisms protection. In addition, organisms produce a multitude of low-molecular-mass compounds, known as secondary metabolites, not only they have roles in cell protection mechanisms but also contribute in range of cellular

processes, such as transcription, development, and intercellular communication.
among these metabolites can be mentioned to Glycerol, erythritol, ribitol, arabinitol, xylitol, sorbitol, mannitol. Galacticol, trehalose, glutamic acid, alanine (4, 2 and 25). (4, 2 and 25).

3. 8.3 High-osmolarity glycerol (HOG) and glycerol pathways in fungi:

HOG pathway is induced in response to changes the environmental water for achieving the best intracelluar osmoregulation . Yeast cells adjust inside activities to optimize survival and proliferation. The transductions of water changing stimuli signal is exerted through multiple mitogen-activated protein kinase (MAPK) cascades. The high osmolarity glycerol (HOG) MAPK pathway is activated by increased environmental osmolarity, high temperatures, evaporation of water, UV radiation, low oxygen concentrations, nutrients and results in a rise of the cellular glycerol concentration to adapt the intracellular osmotic pressure.

Over hyperosmotic shock in S. cerevisiae, Hog1 is rapidly phosphorylated and it translocates into the nucleus. After the cell adapts to the higher osmolarity, Hog1 is dephosphorylated by phosphatases in a negative-feedback approach. Once Hog1p is activated, it coordinates several processes necessary for cellular adaptation to osmotic stress, including ubiquitination, chromatin remodelling, the transcriptional program, mRNA export, translational response, and cell cycle progression. (64 and 65).

The transductions of various extracellular stressors are applied by numerous mitogen-activated protein kinase (MAPK) cascades.
The high osmolarity glycerol (HOG) MAPK pathway is initiated by growing environmental osmolarity. Consequences in a rise of the glycerol concentration adapt the cell to intracellular osmotic pressure (66).

The phosphorylation state of the MAPK Hog1 is controlled by various protein phosphatases. Those include the phospho-tyrosine phosphatases Ptp2 and Ptp3 as well as the phospho-threonine phosphatase Ptc1 (Ptc2 and Ptc3 also seem to play a role, at least when over-expressed).

HOG controls glycerol accumulation in osmoadaptationAs the name states, the probably most important role of theHOG pathway in osmotic adaptation concerns the control of glycerolaccumulation. Glycerol serves as the osmolyte of proliferatingyeast cells . Glycerol is produced from the intermediateof glycolysis, dihydroxyacetonephosphate, into two steps. Those are catalysed by glycerol-3-phosphate dehydrogenase (Gpd1 and Gpd2 in S. cerevisiae) and glycerol-3-phosphatase (Gpp1 andGpp2) , the process has been shown by figure 11 and 12. (25, 2, 26 and 23).

3. 3.8.4 Mannitol:

Unlike glycerol, mannitol is produced not only in cells under salinity stress but also increase under all other environmental stresses which have been examined yet.
In Ascomycota, mannitol has two-step process: fructose 6-phosphate is first reduced to mannitol 1-phosphate by NAD-dependent mannitol-1-phosphate dehydrogenase (Mpd), and then dephosphorylated to mannitol, by mannitol-1-phosphate phosphatase (Mpp) (23) the process has been shown by figure 13 and 14.

3. 8.5 Trehalose

The concentrations of trehalose in Aureobasidium pullulans is enhanced by heat-stressed and salt-stressed cells simultaneously, but not in cells are only just under salt stress.
The biosythesis of trehalose has two-step process: glucose 6-phosphate and UDP-glucose are first turned to α,α-trehalose 6-phosphate by trehalose-6- phosphate synthase (Tps), and transforemd to trehalose by trehalose-6-phosphate phosphatase (Tpp) (67) the process has been shown by figure 14.

3. 8.6 xylitol
All four of the Aureobasidium varieties in their genomes have genes for producing of xylitol as a defend system against osmolality stress, it is noticed a putative D-xylose reductase (cluster 19, 48900/38638, 70467, 36428 and 36838 for A. pullulans var. pullulans, var. subglaciale, var. namibiae and var. melanogenum, respectively). D-xylose reductase transmutes xylose to xylitol, a sweetener compound. The process of producing xylitol for the cell is an interesting commercial process, Which has not yet been thoroughly studied in A. pullulans(23).

3. 8.7 Melanin biosynthesis genes
Black yeasts or sometimes called black fungi, dematiaceous fungi, microcolonial fungi or meristematic fungi (68) produce a black pigment that has long been known to be 1,8-dihydroxynaphthalene (DHN)- melanin which is dark brown or black pigment with a high-molecular-weight, Produced by numerous fungi from various divisions, it has a protective role in various stress conditions, such as

hypersaline conditions. Melanin is the outermost layer of the fungal cell wall or is located within the cell wall structure. Microbes mainly with pathways tyrosinases, laccases, catecholases, and the polyketide synthase pathway produce melanin pigments (23).

3. 8.9 Aquaporins

Aquaporins are large family of major intrisic proteins (MIPs) and has been found in diverse life forms. They act as membrane-channel proteins that transport water (aquaporins) or water plus glycerol (aquaglyceroporins) (69).They provide sufficient water and/or compatible solute fluxes into and out of the cells under diffrents osmotic cases. (figure 13). In organisms water channels and osmoregulators might be vital for survival and adaptability of these polyextremotolerant species in water-challenged environments (23) (figure 15).

Conclusion

Cells being part of a normal tissue or growing in medium culture are always exposed to many internal and external stimuli. Stressors can trigger a variety of stress responses in cells depending on the different types of stressors, severity and duration of encountered stress. Cells either re-establish cellular homeostasis to the former state or adopt itself into condition of the new environment. Responses in cellular and molecular levels to internal or external stressors have become inseparable part of organism's physiology to guarantee the cell survival as well as repair of lesion and replacement with intact cell or eventually death and elimination of damaged cells. (24). Depending on the level and mode of stress, different defense mechanisms and survival strategies are mounted; however, if these are unsuccessful, then the cell death programs are activated to eliminate these damaged cells from the organism (24 and 16). The level of adaptive capacity of a cell ultimately determines its fate (24).

Signal transduction plays the most important role in response to stress. The prerequisite for the operation of a signal transduction system is the complete spatial and temporal identity of all the molecules that make up that system. Thus, there are certain molecules that participate in the modification, delivery, or assembly of signaling components, but do not straightly amplify the signal. Some of them must be proteins which are too critical to transmit signals to the response of stress with high accuracy, these proteins include, Post-translational modification enzymes (such as, methylation, glycosylation, lipidation and ubiquitination of proteins), scaffolds and adaptors, they are paying the most important roles in signal transduction pathways.

General Features of Signal Transduction in all organisms as following:

- ✓ In all organisms, signal transduction mechanisms are highly specific and highly sensitive, and these properties are highly conserved during evolution (70).
- ✓ A wide variety of stimuli (stresses) act through specific protein receptors in the plasma membrane and /or cytoplasm and/or nucleolus. The receptors bind the signal molecule and initiate a process that amplifies (71)
- ✓ The signal, integrates it with input from other receptors, and transmits the information throughout the cell, or in some cases to a local region of the cell (21 and 22).
- ✓ If the signal persists, receptor desensitization reduces or ends the response (72).
- ✓ Multicellular organisms have four general types of signaling mechanisms: GPCRs, Receptor enzymes, Gated ion channels and Intracellular receptors (73).
- ✓ Cells with using second messengers are able to initiate and control the phosphorylation cascade of proteins that eventually activate proteins that are directly involved in the transmission of the signal into the cell or can be targeted transcription factors that bind specific sets of genes related to stress response. (21 and 22)

The initial response to a stressful stimulus in the cell would include helping to defend against the effects of stressors, tolerating harmful conditions with minimal damage to the cell until removing of the damaging agent completely. Though, the cell fails to repel and repair the harmful and damaging effects of the stressors, the cells will enter the death-activating signaling pathway.

In the matter of fact the cell viability depends heavily on the ability to respond appropriately to peripheral or intracellular stress stimuli may provide an answer to this fundamental question, why these responses are highly conserved during evolution in all domains of lives?, alsostudies have shown that these mechanisms are largely driven by a similar mechanism for instance, antioxidant defense mechanisms against oxidative stress or response to drastic changes in physical and chemical conditions such as pH or temperature may be activated mechanisms such as accumulation of heat shock proteins. Antje Gerloff-Elias 2006 demonstrated that heat-shock proteins might play a key role in the adaptation of unicellular green alga to their extreme environment such as pH and temperature. results show In these environments heat-shock proteins

accumulation are increased at extreme pHs levels and does not lead to any change in intracellular pH, indicating an environmental adaptation of increased significantly with accumulations of heat-shock proteins (44).
Types of heat shock proteins are subdivided into ATP-dependent or Independent and Hsp70, Hsp90 and Hsp60 and mediate essential activities such as protein folding, localization and degradation accompanied by co-chaperones and byproducts. Heat shock proteins are mainly synthesized by stressors such as heat, cold, congestion and anoxia that depend on the physiological status of the insect, heat shock proteins have a common function, often interacting with other proteins through networks which are involved in maintaining cellular homeostasis(44 and 45). All of these reactions take place in different organisms from a single cell up to an evolved creature with billions of cells almost in similar approaches (21, 22 and 5).
Prominent examples of perturbations that induce cell stress include DNA-damaging agents (for example, ionizing, radiation and some xenobiotics), which activate repair pathways specific for different types of genetic lesion (7 an 8). Heat shock or chemical toxins that cause protein denaturation, both of which activate the unfolded protein response (UPR) in the endoplasmic reticulum (ER) and mitochondria. hypoxia, respiratory poisons and xenobiotics that cause mitochondrial stress (25).

One of the most problem for understanding the response to stress is, overlapping between differrent stresses and their signal transductions, for example in plants which are under abiotic stress and pathogens simultaneously, major stressors limiting plant growth and productivity worldwide, their interaction is poorly understood due to The reactions to pathogens (biotic stress) may be have take part with other abiotic tension, and reactive oxygen species (ROS) and stress hormones display central nodes in the interacting signaling pathways. generally, abiotic stress does not have positive effects on plant susceptibility to disease (4) (4)(figure 13)

Stressors could have several detriment to intracellular macromolecules including proteins, Nucleic acids and lipids and lead to the cell reparation either cell death.
Stress with less severe effects can lead to alter cellular responses to subsequent environmental signals [1].
Four basic types are to responses in stress condition, they include (1) induce cell repair mechanisms, (2) enforce cell responses that result in impermanent adaptation, (3) initiate autophagy or at the end (4) operating the cell death (8 an 10).
In animal cells, several stress reactions can be clearly distinguished, including DNA damage, oxidative stress, heat shock and unfolded protein responses are common and eventually if the cell is unable to cope with stress-related damage; the stress response can lead to the mechanisms of cell death.

Adaptability levels in plant and microorganisms have three levels: first, plasma membrane and cell wall: Composition, structure enzymes and proteins. Second, Cytosolic and molecular adaptability: salt-in'' strategy (not in fungi), ''salt-out'' strategy, ''compatible-solute'' strategy, '' signal-transducing systems ''. And finally, regulation and expression of genes (4, 10 and 14).

On the question of whether stress in the organism leads to the induction of the death mechanism or takes the way of coping with stress depends to a set of different factors such as cell type of tissue and site of injury, The type of stimulus and the intensity of stress and finally Internal or environmental factors (74).

Purposeful use of biological stressors from bioremediation to ameliorate diseases

It is envisaged that the unpleasant cellular stress responses are entirely related to many prevalent diseases. The wide understanding of the molecular mechanisms of signal transduction and their response help us to involvement in these processes and the design of new drugs, the better performance of plants which used in agriculture in stressed environment or exploiting organisms in three domain of life in bioremediation, etc. For example, depending on the desired outcome, such a response to cell death will modify survival programs or vice versa (90).

Because aberrant cellular stress responses are tightly linked to many common diseases, a better understanding of the underlying molecular mechanisms is expected to enable us to interfere with these processes, for example, to switch such response from cell death into survival programs or vice versa, depending on the desired outcome. In addition, new insights into the mechanism basis of stress responses will open new perspectives for the development of molecular targeted treatment approaches and thus have a great potential for drug discovery (8, 10, 19, 7 and 8).

It is comprehended lately that pathological stress responses are common in organism diseases with a lot of symptoms. First, stress irritants may be too powerful to tolerate therewith allowing insufficient time for amelioration to the normal condition. Second, a cell's capability to manage physiological levels of stress may be had similar results in noxious outcomes and modified in disease level circumstances (91).

As obsessive cellular stress responses are strongly associated with many common diseases, it is expected to have a better comprehension of the underlying molecular mechanisms that allow us to intervene in these processes related to the outcome. In addition, new visions into the mechanism of stress responses will open new outlooks for the advanced molecular targeted therapeutic approaches and have good potential for drug discoveries (3, 24).

In human some affection of Oxidative stress like Parkinson's disease produce harmful oxygen species that may be caused by various conditions, such as genetic mutation and exposure to the environment with biological stress or due to the process of aging of the tissues in the brain cells themselves. There is some evidence that there are some cellular mechanisms to prevent or against Parkinson's disease using oxidative stress reduction mechanisms (46). Another example is abnormal proteins. Nevertheless, more precise analyses containing in-vitro studies have been defined constitution and agglomeration of abnormal forms of alpha-synuclein that oxidized and nitrated as consequences of oxidative stress. These abnormal protein species have detected to be exclusively itinerant and more amenable to move from donor to recipient cells (56 and 46).

As mentioned above about CD73, Studies show that Results with small molecule inhibitors, or monoclonal antibodies targeting CD73 in murine tumor models, suggest that targeted CD73 therapy is an important alternative and realistic approach to effective control of tumor growth. In particular, it helps T-cell–based therapy by enhancing the adaptive immune response machinery, which may increase the function of tumor-infiltrating T lymphocytes, and subsequently lead to improved survival in cancer patients (94). As the link between CD73 and resistance to some antitumor therapy, combining anti-CD73 treatment with chemotherapy or immunotherapy may be an effective approach for these patients with high CD73 levels. In the future, while in the coming age of individual cancer therapy, CD73 expression in cancer patients may be served as a detectable gene marker to choose and use applicable drugs for cancer treatment (96).

At the end it must be motioned that understanding of stress, response and defense in organisms deeply, will lead us for developing our knowledge about organism`s life and its relationship with its environments also seems to be inevitable for future studies (119). Multi-omics approaches comprising genomics, transcriptomics, proteomics, metabolomics and phenomics help us to have comprehend integrated studies on animal, plants, microbes and their responses to external environment and generate multi-layered information that can answer what is happening in real-time within the cells under stress condition(120). These acquired knowledge with using bioinformatics tools can be exploited for prediction and modeling of behavior the cell and interactions with environment under stressed condition with in silico world (virtual cell) for designing new medicine for diseases, pesticide and herbicide With minimal damage to the environment, applying biological elements to biological control, manipulate plants to tolerate tough environment and use them in agricultural of other organisms in extreme situation for bioremediation (92 and 93).

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