Review Paper:

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

Hariri Akbari Farhad
Department of Biology, Biotechnical Faculty, University of Ljubljana, SLOVENIA
fh9572@student.uni-lj.si; farhad.haririakbari@student.uni-lj.si

Abstract
Stress in psychology and biology is defined as any pressure that elicits a response from an organism. Whether cells encounter stresses; the response can be very different from their environment, duration and 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 activating survival paths to starting damaged cell elimination progress. The most crucial roles in responding to stress are played by Signal Transduction Systems. Three domains of lives respond to different stresses and/or stressors include; DNA damage, the unfolded protein, mitochondrial signaling stress, proliferation or elimination of damaged cells responses.

In general, there are levels for defending against stressors (1) plasma membrane and cell wall, (2) cytosolic and molecular adaptability such as salt-in, salt-out and Compatible solutes strategies and (3) finally gene regulation.

In this review we are going to discuss stress in four aspects: (I) Principles of stress, (II) fundamental mechanisms of the stress response and (III) the relationship between response to stresses and defense mechanisms in three areas of life and (Iv) at the end using stress responses to ameliorate diseases and other applications.

Keywords: Abiotic and Biotic stresses, Stress Response, Signal Transduction System, Defense Mechanisms and Diseases.

Introduction

Every organism is shaped by its environment. From tiny bacteria to an elephant or a whale weighing 200 tons and fungi that extend for hundreds of hectares underground. The diversity and breadth of life on Earth are striking in its strategies for proliferation and reproduction process. Organisms inhabit nearly every environment on Earth, from the warm, deep valleys on the ocean floor to the Arctic ice. Each environment presents both resources and limitations (stressors) that shape the appearance and function of organisms.[28,56,118]

Stress, in psychology and biology is environmental or physical pressure that elicits a response from an organism,[35,44] in other words, any factor that seriously threatens homeostasis in Oregon[111]. In most cases, stresses boost survival because it forces organisms for adapting and/or changing environmental or internal conditions rapidly[35,44]. The threat or stimulus is described as a "stressor" and response to a tension is called "stress response"[111].

Multi-omics studies and integrated approaches including genomics, transcriptomics, proteomics, metabolomics on organism under stressed situation can help us to have a better comprehension of organism responses to internal or external stressors also, their relationships and interactions[44]. These studies will lead to procreate multi-layered information that can answer what is happening in real-time within the cells and its interaction with the surrounded environment under stress conditions.

In this review we are going to discuss stress in four aspects: (I) principles of stress, (II) fundamental mechanisms of stress response and (III) the relationship between response to stresses and defense mechanisms in three areas of life and (IV) at the end using stress responses to ameliorate diseases and other applications to improve the environment.

Basic principles of stress

As far as physiology has been concerned, Stress is a known factor which has led to evolution of ecosystems from the beginning of life. The ability of organisms to withstand stress is the most important key to survival in rapidly changing environments; the organism must have mechanisms for sensing and responding to changes in its surroundings. Organisms constantly adjust their internal chemistry (homeostasis) to this variation by internal adaptation or location changing in their environment[35,93].

In spite of the advantages of stress, in biotic communities, stresses may cause loss of biomass, impoverishment of species, or degradation in tough environmental conditions. Stress is usually an important factor in reducing the organism's potential when it exceeds the biological tolerance threshold, therefore it may constrain or restrict the development of organisms in their ecosystems[9,93].

Table 1
Some examples of the most important stress types in biology

	Ellement of stress	Type of stress	Explanation
Abiotic	Water	Deficit Drought Flooding Anoxia Osmosis	Water stress is one of the most important abiotic stresses which affect living organisms, each organism requires a certain amount of water to have optimal condition. too much water leads to flooding stress. cells swell firstly, then burst. Eventhough, too little water turns to drought stress that caused the living organism to dry up. This condition is called desiccation. Both of these conditions are deadly effcts for living creatures.
	Temprature	Cold Chilling Freezing Heat fire	Temperature stresses can also be harmful to many living organisms which need to be in an optimal temperature range to have the best growth and proliferation. If the temperature drops sharply or quickly leads to cold stress or chilling stress. Also, Extreme forms of cold causes freezing stress. Cold stress reduces the absorption of water and nutrients, which eventually results in drying, desiccation and starvation in the cell. Under these conditions, the soluble constituents in the cytoplasm can be completely frozen and eventually lead to cell death. Heat can severely affect living things and destroy proteins this process is called denaturation. High temperature melts cell walls and membranes and affects permeability. Burning of living organisms directly with fire breaks down cell structure and other internal components completely.[12]
	Light	Low high radiation	different kinds of light stress encompassing light quality, type, Changes in their intensity, range and duration can lead to acclimatory responses, cellular damage and ultimately to the death of living organisms.[14]
	Chemical	Salinity Mineral deficiency fertility Toxicity Acida base Air pollutants Ozone Sulfur Dioxide NOx oxide CO2 – co Heay metals Pesticide pH levels Oxidative Ionizing Xenobiotic	both in deficiency or in large quantities of Pesticides, herbicides, Organic and chemical fertilizers, imbalance of nutrition, toxicity can cause stress in the living organism. in High amounts of salt in cytoplasem can lead to cell desiccation, as well as elevated levels of salt outside cell membrane will cause water to leave the cell, with a process called osmosis. when living organisms grow in soils fertilized with improperly composted or sewage sludge can absorb heavy metals. High heavy metal interubt basic physiological and biochemical activities of the cell such as photosynthesis.[18]
	Physical	Pressure Wind Mechanical touch	Mechanical induced stress (MIS) is defined as in general exposed to rain, flood, earthquake or by other creatures such as animals with various acts such as rubbing, stabbing or in plants bending the stem, etc. Fore example, the wind with affecting on transpiration of water from stomata of leaves is caused desiccation of eater and decreased the rate of photosenthesis.[20,50]
	Nutrients	Fertilizers Starvation	Nutrient stress (deficiency or excess) seriously affects living organism prolifaration[20].
Biotic	living organisms	fungi nematodes arachnid bacteria insects Viruses animals weeds	This type of stress determiend as a stress which is caused by other living organisms such as fungi, bacteria, viruses, parasites, weeds, insects etc.[1]

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[36].

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[44,45].

Type of stresses: Generally all the organisms depend on environments that surrounding them have been affecting by two types of stress which are called abiotic and biotic stresses[44,45]. They are causing the most major effects on organisms and important stresses in biological realm have been shown in table 1. Most organisms live in ever-changing environments, the ability of cells for receiving and responding to 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 decide their fate in the future[29,69].

Stress response fundamental mechanisms

Cells perceive permanent information as signals from the environment by membrane proteins which 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 the move toward food, escape from toxic substances or the formation of dormant spores in a nutrient-depleted environment[73].

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 the appropriate interdependent metabolic activities be accomplished in different tissue generally or exclusively targeted one cell.

Plant cells respond to various hormones, stimuli, or changes in environmental stress factors. In all of these examples, signals display information detected by particular receptors and transformed to intracellular chemical responses. All of these processes which converted information into a chemical changes are called signal transductions and they are universal property of all living organisms in biology territory[29,69].

General Features of Signal Transduction: Biological functions are responses to hormones and growth factors, the senses of light, scent and taste; the transmission of nerve signals and cell cycle controllers. Phosphorylation of a few specific target-cell proteins is often the end result of a signaling pathway that changes their activities and therefore cell functions. Biological signaling pathways are essential mechanisms of signal transductions and adaptation of each living organism in wide range of organism activities[24].

Signal transductions are highly complicated, sensitive and extremely specific achieved by the precise molecular complement state between signal molecules and their receptors[32]. There are three factors that are responsible for the extreme accuracy of signal transduction: the high affinity between receptors and signal molecules[105], cooperative in the ligand and receptor interactions (often but not always)[34], amplification of the signal by enzyme cascades[35].

Thus, there are 6 common components involved in every signal transduction systems they have been illustrated in figure 1. In figure 2 as an example, it has been shown all components of signal transduction in the Sho1 branch have key roles in the HOG pathway (high-osmolarity glycerol pathway) in yeast and other halophilic and halotolerant fungi.[67,77]

Signaling pathways are mainly composed of chain proteins which are conserved and protected during evolution. In this process, proteins interact with each other in a specific sequence that is related to the previous sequence. Generally, every organism has in common the important mechanisms of intracellular signaling; in spite, some components are dominant and general; others have specific pathways, so unique results are obtained in each organism.[67,77] If discussed in the realm of biology in general, each organism has four types of signaling mechanisms (figures 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 through 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). Common types of cell receptors showed in figure 1.

As illustrated in figure 1 and 2, extracellular signals may belong to various mineral or biochemical molecules, they can be short or distant, 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[67,77]. 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.[8,67,77] In summary, cells require to participate in five subunits of intracellular signaling pathways simultaneously or approximately sequentially during the cell division and proliferation cycles as shown in figure 3.[32]

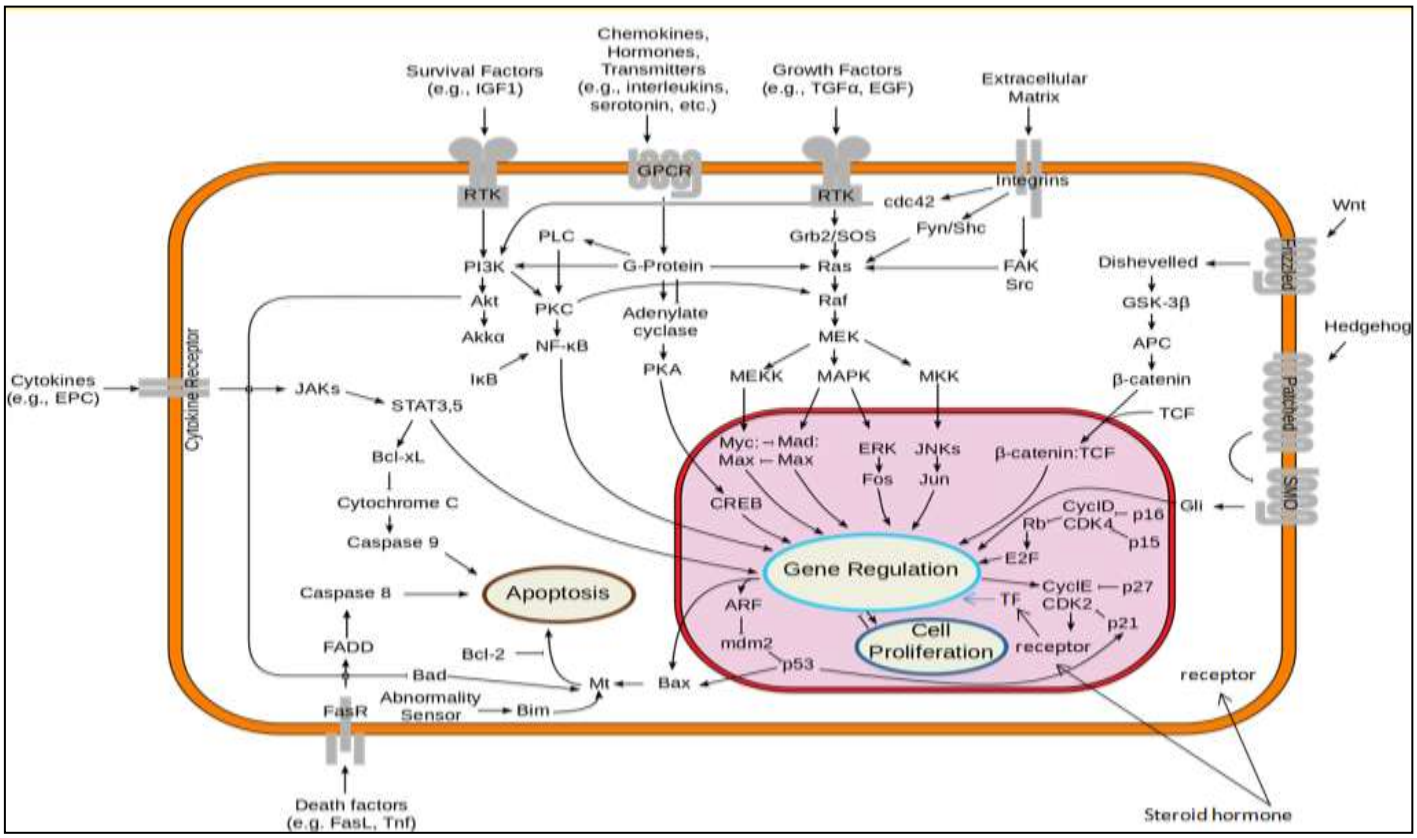

Figure 1: All component which are common in every signal transduction pathway

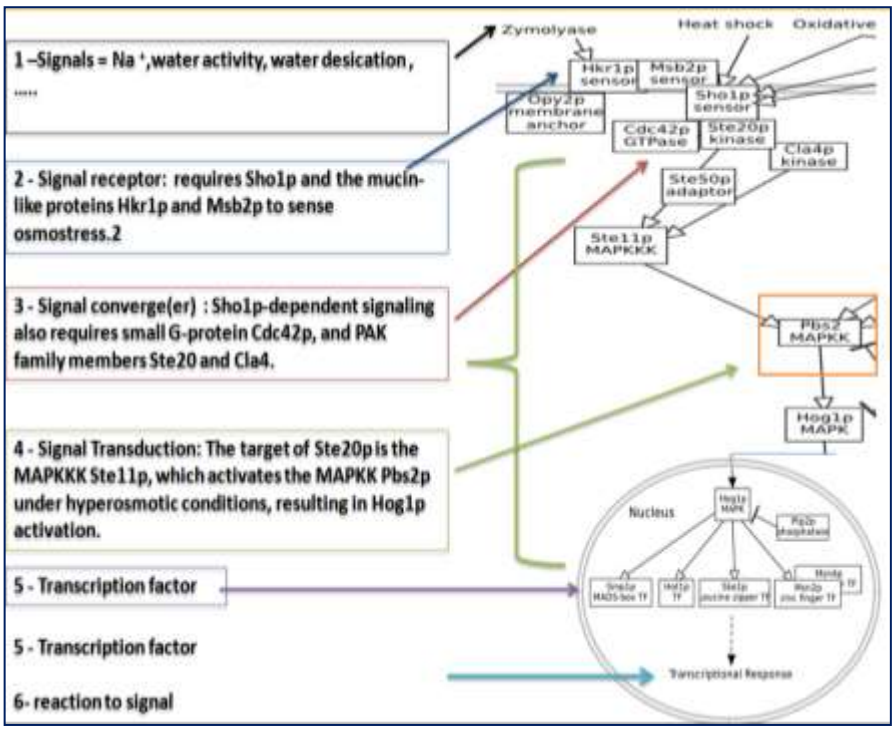

Figure 2: All component of signal transduction in the Sho1 branch

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 O_2, nutrients, light, harmful chemicals and so on[67,77]. Step 2 illustrates reception of signals; the intracellular components of the signal transducer are very particular to receptors, thus maintaining the specificity of the input signal within the cell[55]. 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[61]. 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 activate or deactivate other enzymes, so the message transfer cascade can be continued[81]. 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 subunit, directly or indirectly, is associated with other pathway subunits leading to the physiological effects of proliferation or cellular activities[67,77].

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.[33,34] 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 are shown as step 4 in fig. 2. 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 2)[18,33,61].

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

Some common examples of perceive, transduction and response to stress in cellular and molecular level in three domains of life are called Archaea, Bacteria and Eukarya cells[34].

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 ligand. 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 and then produce a biological response to the signal.[22,67,77,93]

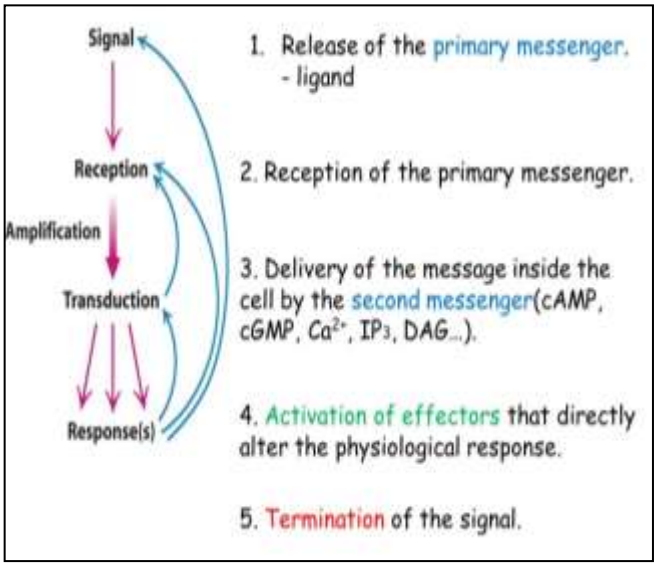

Figure 3: Signal transduction depends on molecular circuits

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

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 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, cytoskeleton 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[62,77,106]. The process of the apoptosis is highly protected during evolution and executed a major physiological obligation in development, proliferation and aging of organisms[29,67,77].

The morphology of cells undergoing apoptosis is completely different from the morphology of cells associated with necrosis or phagocytosis.[26] 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 activates 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) demonstrated to play a key role to compel programmed cell death in mammalian cells.[27,54,62]

Caspases are defined as a family of cysteine proteases that contribute as death-affecting molecules in miscellaneous forms of apoptosis. They are synthesized as inactive pro-enzymes, after activating, 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 and the process has been shown in figure 4.[29,62,67,77]

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.[27,54,97]

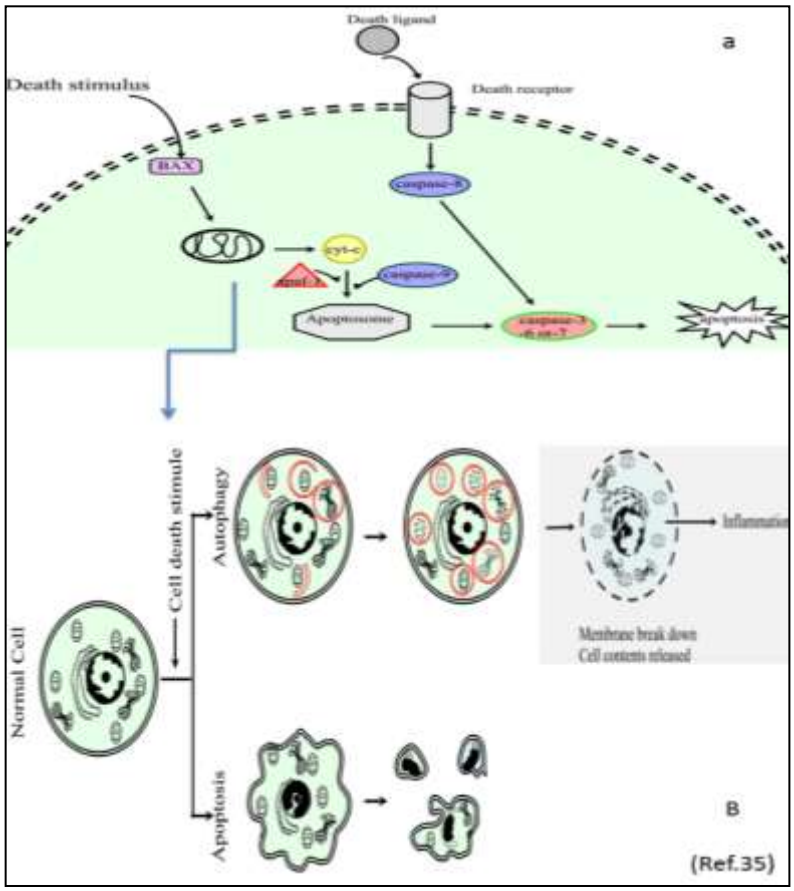

Figure 4: The programmed cell death process of apoptosis and autophagy[35]

This process has several steps that are determined by the vesicular decomposition destruction of long-term cytoplasmic proteins and organelles, for instance, mitochondria. This process is driven by applying of lysosomes and promotes which can survive during starvation periods, as the cellular energy level can thus be maintained. Within autophagy, double-membrane vesicle is denominated as autophagosomes are procreated. The first step for deciphering autophagy found the Atg gene in yeast. Subsequently, in humans, further advanced studies have been made for understanding the molecular mechanisms involved in controlling in 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 (97 and 57). 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 acting as a stressor coping approach that inhibits cell death, but in some situations, this would be an alternative pathway to cell death.

The intricate relationship between autophagy and cell death confirms that the response to stressful conditions is somewhat linked at the molecular and cellular level. Finally, it should be noted that important cellular molecular events are in stressful conditions which ultimately determine whether autophagy is a protective or destructive method but the process has not yet been fully defined[29,67,77].

Necrosis: Necrosis, is a term generally used by pathologists related to any death 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 the owned damaged cell**.** Necrosis in multicellular organisms has long been regarded as an uncontrolled, unregulated and random process of cell death and therefore, there is now evidence for a set of signaling pathways regulating necrotic cell death. Morphologically, necrosis is associated with increase of the cell volume, organelle swelling and rupture of the plasma membrane; results are loss of internal content and cell death. Manifold signal transduction cascades have been determined involved in the process of necrotic cell death.

There are a lot of studies which have proved that serine / threonine kinase RIP1 can be one of the significant 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.

ER is the main major intracellular calcium storage; mitochondrial calcium has been determined to induce oxidative phosphorylation, oxidative phosphorylation leading to production of more generation of ROS. Cellular integrity is destroyed by damaging the organelles and macromolecules in the cytosol by both ROS and calcium leading 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 or/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[29,36,69].

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 reactive 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[107]. It leads to major cytological changes, such as decreased or vanished mitochondria cristae, a ruptured outer mitochondrial membrane, condensed mitochondrial membrane[70,124].

This process starts with an iron-dependent cumulation of lethal ROS in cells that leads to induce the erastin which inhibits the cellular uptake of cystine and then blocking the intracellular antioxidant defense mechanism by limiting the production of intracellular glutathione (GSH), one of the major cellular antioxidants.

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 5. [37,38,119]

NETosis and Etosis: NETosis (NETs) in 2004 was defined as one kind of cell death. NET is a new preventive cell approach and distinct from apoptosis as well as necrosis or Ferroptosis[40]. 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 various types of immune system cells reporting

that release chromatin and granular proteins into the extracellular space, then creating DNA traps[20,21]. NETosis is a cell death associated with neutrophils, which is described by the formation of large network-like structures outside the cell.[21,49,109] Other cells such as eosinophils, mast cells and macrophages, can have similar result in cell death. afterwards, the process has been changed to ETosis, which means releasing of extracellular traps (ETs) (figure 6).

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 disintegrating, then granules and the composition of the nuclear or organelle components are released into the cytoplasm[21,47,49]. NETs can protect the cell from broad-ranging biological pathogens 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 be able to initiate NETos is (figure 6)[21,109].

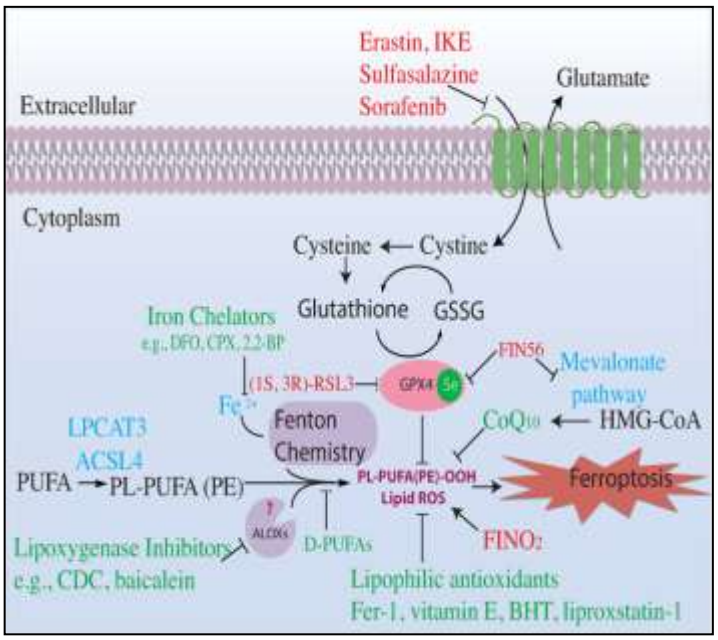

Figure 5: Ferroptosis process

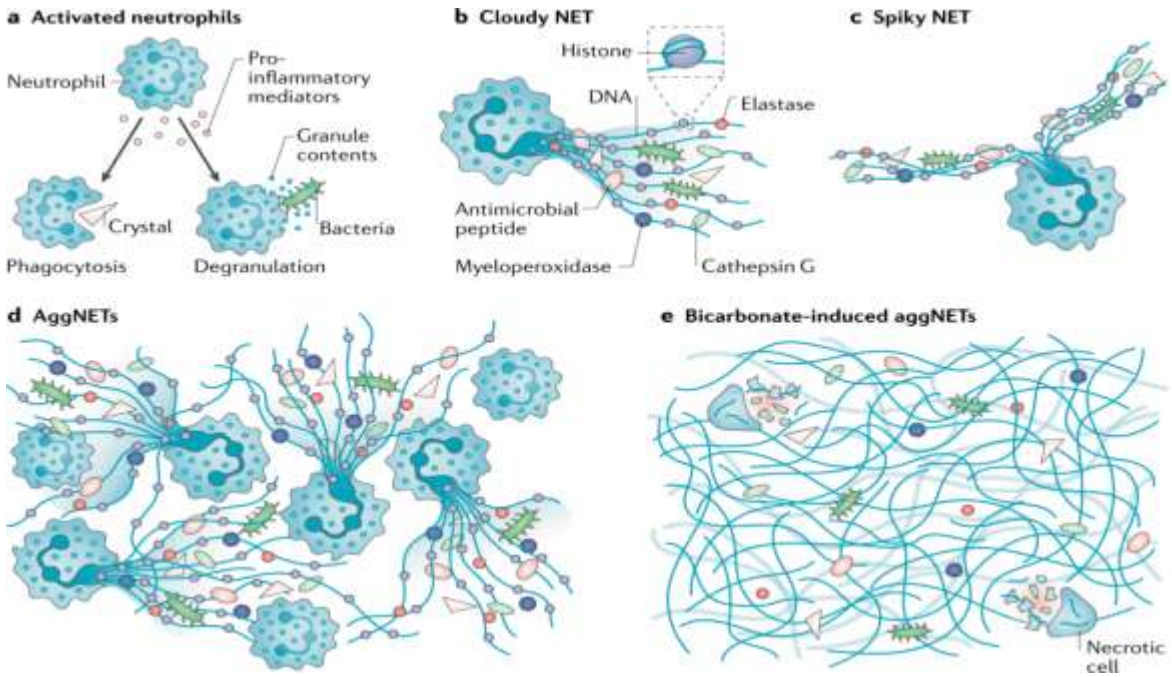

Figure 6: NETosis and Etosis protect the host cells against biological pathogens by methods such as the generation of neutrophil extracellular traps (NETs), phagocytosis, the formation of reactive oxygen species (ROS) and releases antimicrobial from vesicles (degranulation)[122]

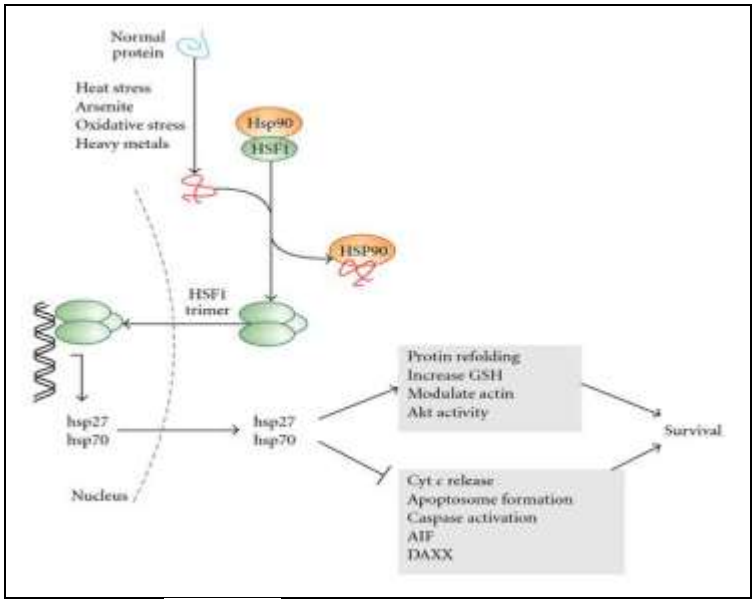

Figure 7: The Heat Shock Response

The Heat Shock Response: The Heat Shock Response is one of the majour survival cell activities which was initially described as a biochemical response of cells to stressors like temperature rises above normal. It has been discerned that a lot of stimuli as well as oxidative stress, pH and heavy metals activate this response too. One of the major outcomes of stressors on the cell is the damage to proteins as well as accumulating unfolded proteins[14,83].

In order to neutralize these phenomena, cells try to increase the expression of chaperone proteins that collaborate to refolding of misfolded proteins and decrease protein aggregation; this mechanism is a temporary protection approach and form conditions that are identified as heat tolerance. Therefore, when the cells are exposed to distinct stress statuses, not only just if the temperature rises, but also in other statues such as oxidative stress, anticancer drugs, heavy metal, etc. become more resistant.[36,67,77]

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 called heat shock factors (HSF).[67,77,83] When the cell is under stresses like oxidative, 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[36,67,77,83]. The relationship between the unfolded protein response pathway and the heat shock response in the endoplasmic reticulum has been indicated in figure 7[111].

ER stress leads to the unfolded protein response: Proteins in the endoplasmic reticulum (ER) are synthesised and can be modified by posttranslational processing as well as glycosylation, lipidation, carbonylation, the formation of disulfide bonds, promote protein correct folding, oligomerization etc. This process leads to produce mature proteins which have more effective structure to do cell goals or secrete out[30]. 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 Ca^{2+} homeostasis, starvation, oxygen deprivation or proteins glycosylation blockage that caused accumulation of unfolded proteins in the ER leading to ER stress.[36,67,69,77]

Meanwhile endoplasmic reticulum (ER) is under stress leading 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 exploited out for activating ATF6. XBP1 is of the ATF6 target genes. Ire1 catalyzes the alternative splicing of XBP1 mRNA that caused 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[36,67,69,77] (Figure 8).

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[42,104]. These factors are categorized as physical, chemical or biological elements by table 2. They lead to mutations or cancer by damaging cellular DNA (table 2)[36,79,90]. DNA damage response (DDR) happened while DNA doubles (DSBs) or single (SSBs) strand break (DSBs) are mentioned as key lesions that induced the initiation of the DDR[5,7,85].

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.[36,77,103]

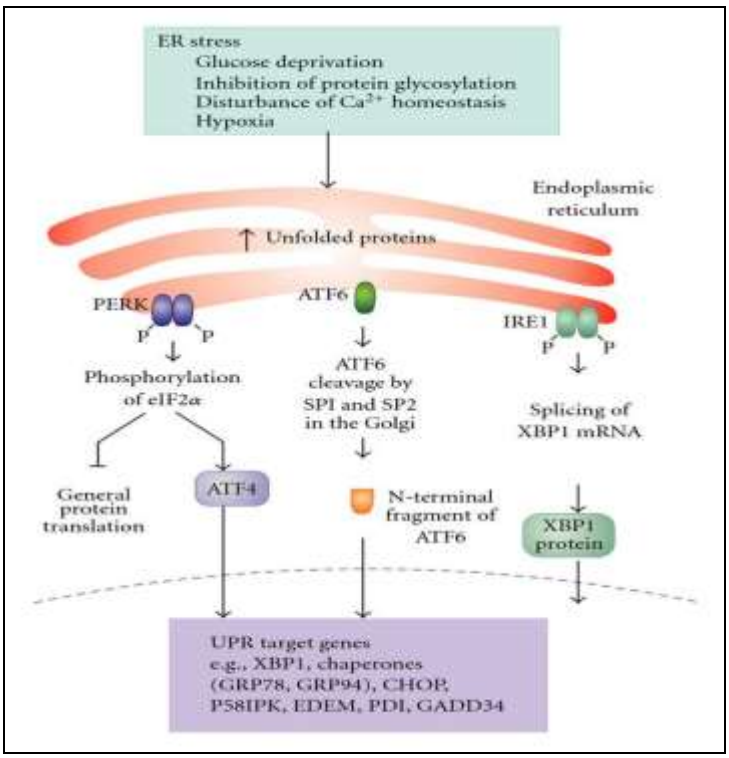

Figure 8: ER stress leads to the unfolded protein response

Table 2
DNA damage factor

Agents	Effects	Examples
Direct Acting (Alkylating and acylating)	Inhibition the growth of the cell. Initiation of programmed cell death mutations. incidence of cancer carcinogenic mutations	include: β-propiolactone, Dimethyl sulfate, Diepoxybutane, Anticancer drugs (cyclophosphamide, chlorambucil, bleomycin, nitrosoureas, 1-actyl-imidazole and Dimethylcarbamyl chloride
Indirect Acting **(**Acylating)	Covalent bonds with DNA and prevent replication. carcinogenic mutations	Benz(a)anthracene Benz(a)pyrene (1st chemical carcinogen to be discovered) Dibenz(a,h)anthracene 3-methylchloanthrene 7,12-Dimethylbenz(a)anthracene.
Natural Plant and Microbial Products	incidence of cancer hives, fever, swelling of tissues neurological problems vomiting, nausea, abdominal pain	Aflatoxin B1 [Group 1] Griseofulvin Cycasin Betel nuts
Metabolic reactions	single and double strand breaks depurinations, depyrimidinations, double-strand breaks, O6-methylguanines cytosine deamination	reactive oxygen species, reactive nitrogen species, reactive carbonyl species, lipid peroxidation products and alkylating agents
Environmental	Oxidative damages single and double strand breaks	UV light ionizing radiation

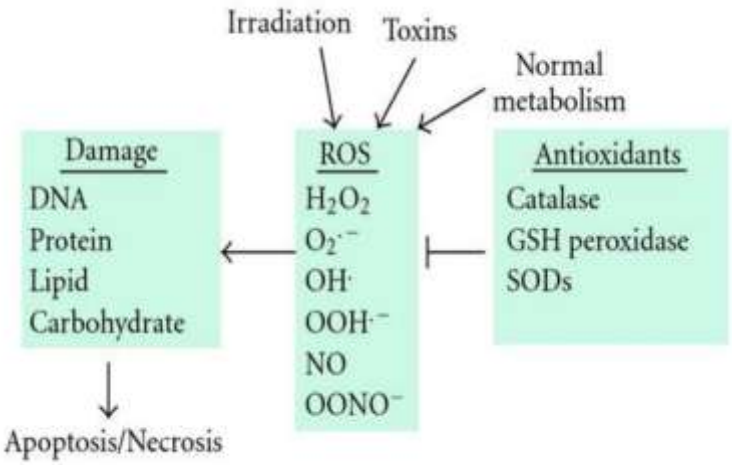

Figure 9: Oxidative Response elements and results

Table 3
Major alkali metal-cation transporters in halotolerant/halophilic microorganisms

Description	Transporters identified in halotolerant/ halophilic microorganisms

halophilic microorganisms.

Description	Transporters identified in halotolerant/ halophilic microorganisms	
K^+ efflux channel	Tok1 :	*Hortaea werneckii*
		Aureobasidium sp.
K^+ uptake uniporter	Trk1,2 :	*Hortaea werneckii*
		Wallemia ichthyophaga
		Aureobasidium sp.
		Debaryomyces hansenii
	DhHak1 :	*Debaryomyces hansenii*
	Trk AI :	*Halomonas elongata*
	TrkAH :	*Halobacterium salinarum* NRC-1
		Halococcus hamelinensis
		Halomonas elongata
	TrkA2 :	*Halomonas beimenensis*
$K^+(Na^+)$ efflux antiporter	Hak1 :	*Aureobasidium*
		Debaryomyces hansenii
K^+ efflux P-type ATPase	Acu :	*Wallemia ichthyophaga*
		Aureobasidium
Na^+ efflux antiporter	Nha1 :	*Hortaea.werneckii*
		Wallemia ichthyophaga
		Aureobasidium sp.
		Debaryomyces hansenii
	NhaC :	*Halobacterium salinarum* NRC-1
Na^+ efflux P-type ATPase	Ena1,2 :	*Hortaea werneckii*
		Wallamia ichthyophaga
		Aureobasidium sp.
		Debarymyces hansenii
	Na^+ P-type ATPase :	*Dunaliella maritima*
Na^+/P_i symporter	Pho89 :	*Hortaea werneckii*
		Wallemia ichthyophaga
		Aureobasidium sp.
		Debaryomyces hansenii
H^+ exporter P-type ATPase	Pma1 :	*Hortaea werneckii*
		Wallemia ichthyophaga
		Aureobasidium sp.
		Debaryomyces hansenii
Na^+/H^+	Nhx1 (late endosome) :	*Hortaea werneckii*

Ref. 2

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[103]. 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[99].

Mismatch repair process responsibility is for eliminating of mismatched nucleotides and replacing them 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[36,56,67,77,108,116]. 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[117].

The MRE-11-Rad50-NBS1 (MRN) complex activates DSBs ataxia telangiectasia mutated (ATM) to identify broken DNA also phosphorylates downstream substrates such as checkpoint kinase 2 (Chk2) that eventually phosphorylate p53. If the damage is high intense and cannot be maintained by the cell, pro-apoptotic p53 target genes induced some complex such as Fas, Puma, Noxa and Bax, genes that boost the rate of apoptosis[130]. As an example, serine/threonine-protein kinase ATR also named as ataxia telangiectasia and Rad3-related protein or FRAP-related protein1 in humans are enzymes encoded by the ATR gene. They activate phosphorylates Chk1 and prevent cdc25c to mediated G2/M or alternatively cdc25a prohibitors to promote inhibition S-phase[23,67,77].

Oxidative Response: A range of diverse reactive oxygen species (ROS) has 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 the long-term and cell death program will be started[9,36] (Figure 9).

Stress response leads to cancer: Nucleotides are produced by different types of cells in response to stressful signals like as injury, hypoxia and inflammatory condition etc. In addition, nucleotides are hydrolyzed by the enzyme waterfall as follows: ATP/ADP turns to AMP by NTPDases (CD39) then AMP into adenosine with ecto-5′- nucleotidase (also named as CD73)[13,129], finally adenosine is changed to inosine by adenosine deaminase[120]. Therefore, a series of cell surface-located ectonucleotidases adjusts purinergic signaling.

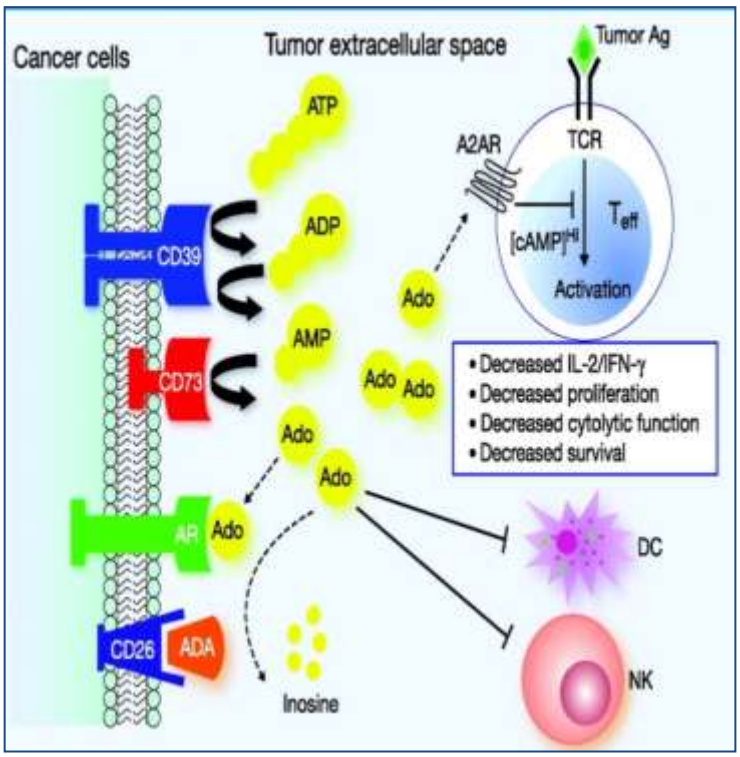

Figure 10: Rules of CD **proteins in cancer**

The equilibrium between ATP / ADP, AMP and adenosine is very substantial in tumor controlling progression[43,94,121]. Cells create a micro-tolerant environment and enable a large number of immune suppression mechanisms which might work in a coordinated procedure to counter effective safety responses[39,129].

In other words, purinergic signaling has emerged as a important phenomenon in the progression of cancer. NT5E gene encodes peripheral protein is called CD73 and has crucial role in purinergic signaling pathways (adenosinergic signaling). CD73 has both enzymatic and non-enzymatic activity in cells. Significantly, the increase in data suggests that CD73 is also a key regulator of cancer progression. The cascade activity of the CD73 enzyme, which accelerates the breakdown of AMP to adenosine[98,110].

Also, it leads to the invasion *in vitro* activity, proliferation and migration, tumor angiogenesis and immune evasion *in vivo* of cancer in cells independently of its enzymatic activity. Although, the non-enzymatic performance of CD73 has not been well studied yet[13,92,121].

Recent findings show a mechanism for suppressing the immune system caused by tumors, where tumor-derived CD73 activities as an ecto-enzyme lead to produce extracellular adenosine and cause acceleration of the tumor development by limiting the antitumor T-cell immunity via adenosine receptor signaling[112,125]. With the important roles that CD73 plays in tumor formation, it has become an attractive therapeutic target for cancer.[64]

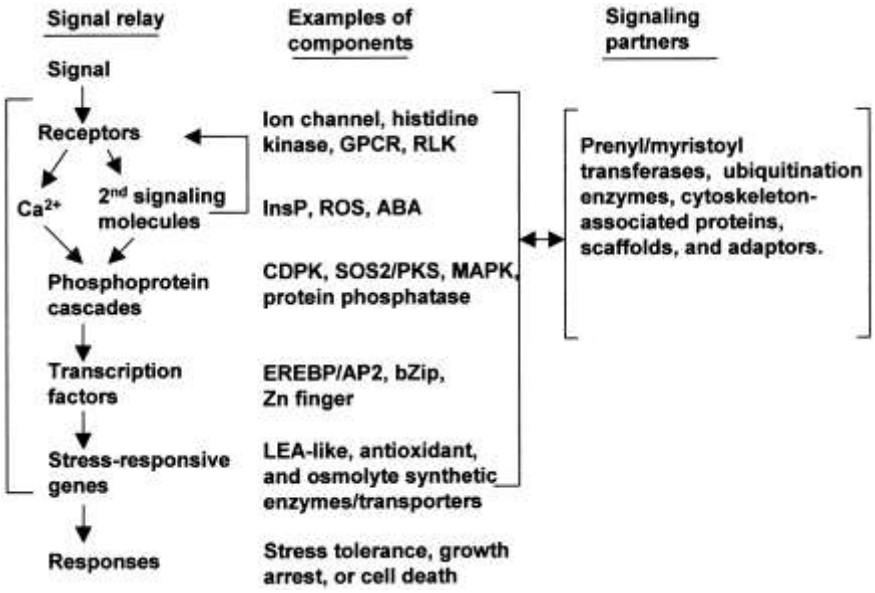

Figure 11 (a): Plant responds to biotic and abiotic at the same time

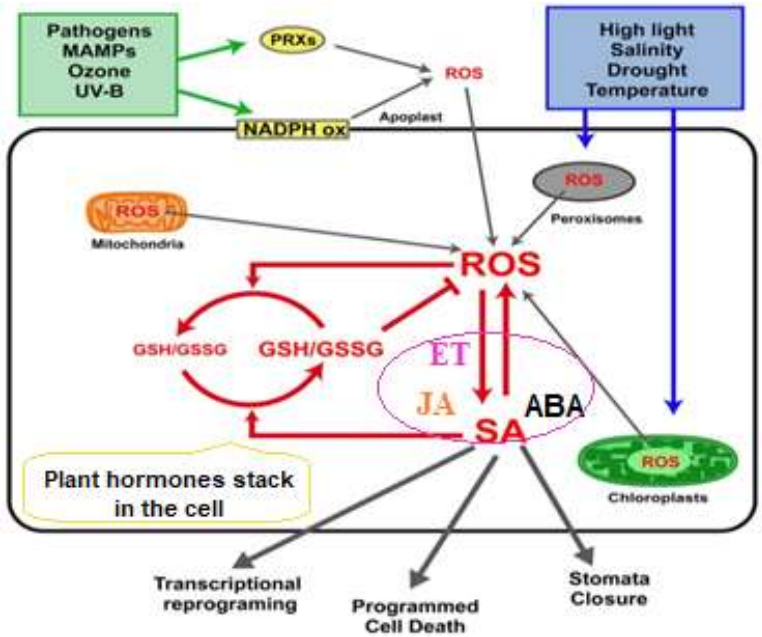

Figure 11 (b): Plant hormones stack in the cell and lead to responses

Molecular function: Studies have shown that CD73 acts as a nucleotide that catalyzes the hydrolysis of AMP into adenosine and phosphate. In particular, adenosine which is created by CD73 plays an important role in tumor immune escape. Beside enzymatic function of CD73, it has functions as a signal and adhesive molecule that can adjust cellular interplay with extracellular matrix (ECM) components such as laminin and fibronectin due to the invasive and metastatic properties of tumor development[65,66].

More importantly, higher levels of CD73 expression are associated with tumor invasion, migration, adhesion, regeneration, invasiveness and metastasis and shorter patient survival time in diffrent cancer.[19,65,90] Upregulated expression of CD73 has been found that had a highly invasive affects on human melanoma cell lines, but not in melanocytes or in initial tumor cells[3].

Biological activity of CD73 (ecto-5′-NT) is perteculary to the enzymatic phospho hydrolytic function on extracellular nucleotides. This ecto-enzymatic cascade changes ATP to adenosine by tandem activity of CD39 (ecto-ATPase) that activates adenosine receptors. In contrast to the intracellular generation of adenosine from cytosolic repository of adenine nucleotides which are catalyzed by cytosolic 5′-NT inside of the cell, generating of extracellular adenosine by CD73 is prevailing tool of producing adenosine. It depends a lot to availability of extracellular AMP[48] (figure 10).

Plants respond to multi stress at the same time (biotic and abiotic): Abiotic stress such as cold, drought, salt and heavy metals are largely harmful and in some cases have 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[44,52]. 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 Ca^{2+} 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[49,52,80]. After diagnosis, the plants' constitutive fundamental mechanisms lead to activate wrapped signaling cascades of defense which varies from one stress to another[55,100]. 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[46,102].

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 for sufficient defense reactions and gain plant tolerance until minimize the biological damage which is caused by the stress. 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[116].

Therewith, plants under stress can be able to show disparate degrees of sensitivity pertaining 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. A 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)[50]. 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 significant stressors among them because it has profound impacts on crop and food productions directly. The limiting factors 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[74].

This phenomenon is termed cross-tolerance and it is noted that plants have a powerful regulatory system that allows them to adapt quickly to a changing environment[60,66]. For example, it has been reported that when factors such as a pathogen infection have accompanied with high salinity in a tomato plant at the same time, the resistance to both of biotic and abiotic stressors can be enhanced[60].

Also, in various agricultural and horticultural products, this type of reaction to both types of stresses has been observed by picking leaves (pruning the plant)[45,95,105]. This type of resistance can be achieved by specific chemical stimuli for instance the resistance inducers BABA (beta-aminobutyric acid) or BTH (benzothiadiazole).

Genetic manipulation brings about the modification of genes and proteins in plants with previous contact with a specific 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[15,44,45,78] (figure 11 "a" and "b").

Defense mechanisms in extremely halophilic microorganisms

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 with increased osmotic pressure and low water activity hence requiring peculiar adaptation mechanisms to salinity stress.[122]

One of the mechaniems which is used 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) 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.[7,84,85] Na^+ is expelled from the cell by Na^+/H^+ antiporters systems. 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 are in halotolerant / halophilic microorganisms in tale 3[6,34,58,68].

Compatible solutes strategy and secondary metabolite biosynthesis: Mitogen-activated protein kinase (MAPK) pathways are accountable in yeast and animals for the 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[85].

Most bacteria and eukaryotic organisms apply mechanism for accumulation ''compatible solutes'' to maintain their intracellular concentration of Na+ under the toxic levels for the cells. The nature of compatible solutes in the cytoplasm is in such a way that it does 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 have been identified 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. Rather, they are involved in a wide range of cellular processes, such as transcription, development and intercellular interactions. These metabolites can be mentioned to glycerol, erythritol, ribitol, arabinitol, xylitol, sorbitol, mannitol, galactitol, trehalose, glutamic acid, alanine[34,68,83].

High-osmolarity glycerol (HOG) and glycerol pathways in fungi: HOG pathway is induced in response to changes in 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 are 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 the adapt the intracellular osmotic pressure[41,65]. Over hyperosmotic shock in S. cerevisiae, Hog1 is rapidly phosphorylated and it translocates into the nucleus[113].

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[12,65].

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[94].

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 osmoadaptation. As 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 12 and 13.[11,26,34,83]

Mannitol: Unlike glycerol, mannitol is produced not only in cells under salinity stress but also increases 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), after that dephosphorylated to mannitol, by mannitol-1-phosphate phosphatase (Mpp);[115] the process has been shown by figure 14.[44,45,124]

Trehalose: The concentrations of trehalose in *Aureobasidium pullulans* is increased by heat-stressed and salt-stressed cells at a same time, but cells are only just under salt stress[123]. The biosythesis of trehalose is done by two-step processes: glucose 6-phosphate and UDP-glucose which are first turned to α,α-trehalose 6-phosphate by trehalose-6- phosphate synthase (Tps), then transforemd to trehalose by trehalose-6-phosphate phosphatase (Tpp),[82] the process has been shown by figure 15.

Xylitol: All four of the Aureobasidium varieties in their genomes possess genes for generating of xylitol as a defend system against heat and salt-stresses, studiese have reported that D-xylose reductase (cluster 19, 48900/38638, 70467, 36428 and 36838 for A. pullulans var. pullulans, var. subglaciale, var. namibiae and var. melanogenum respectively) transmuted xylose to xylitol which is a sweet compound. The process of producing xylitol in fungi is an attractive commercial process in the industry (figure 13)[38,115].

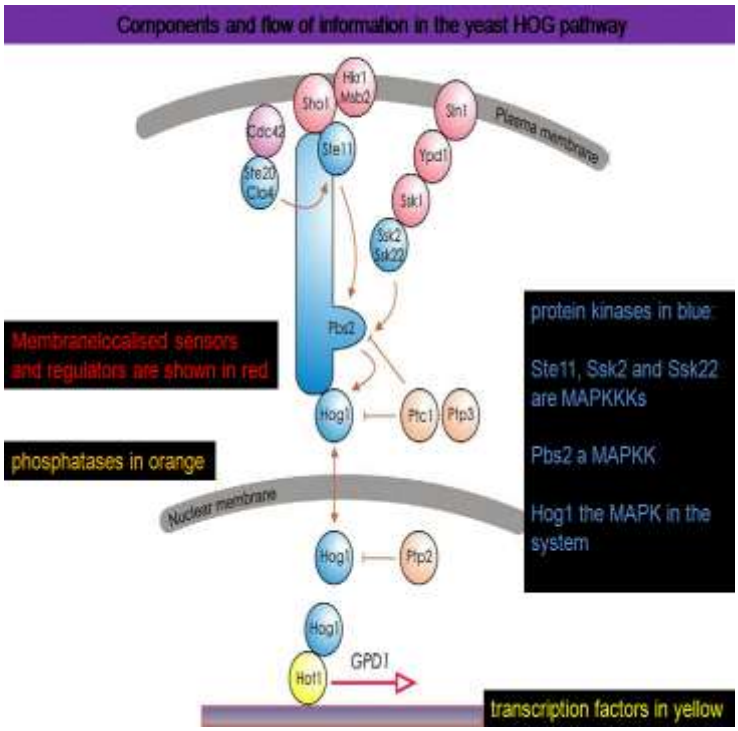

Figure 12: High-osmolarity glycerol (HOG) and glycerol pathways in fungi

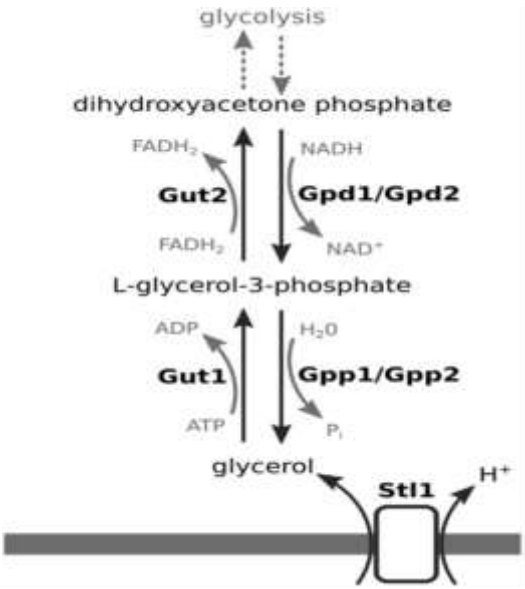

Figure 13: Glycerol is produced from the intermediateof glycolysis, dihydroxyacetonephosphate, into two steps

Melanin biosynthesis: Black yeasts or sometimes called black fungi, dematiaceous fungi, microcolonial fungi or meristematic fungi[91] 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[115].

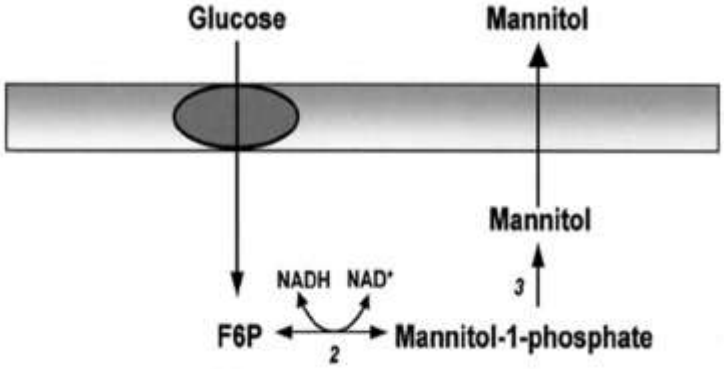

Figure 14: Mannitol is produced by a two-step process

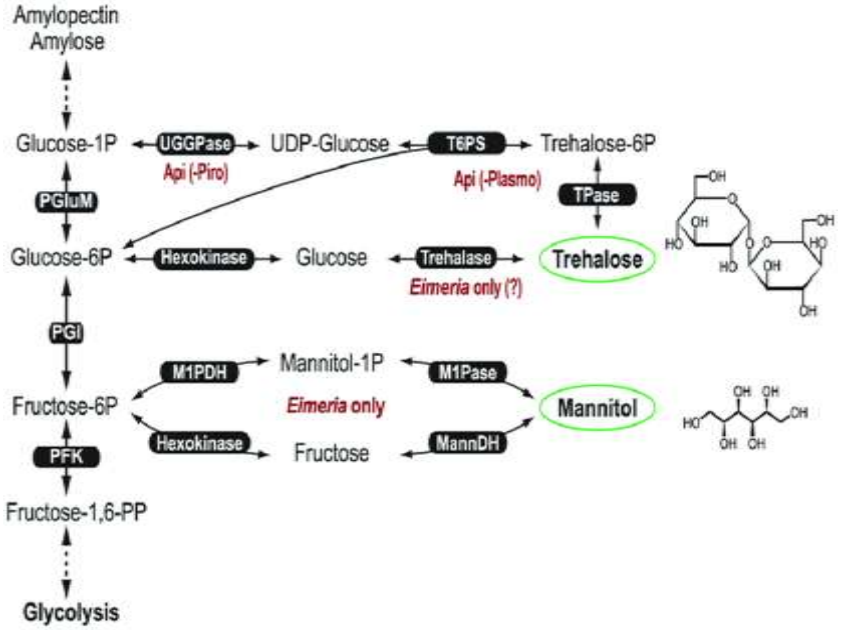

Figure 15: The biosynthesis of Trehalose and Mannitol

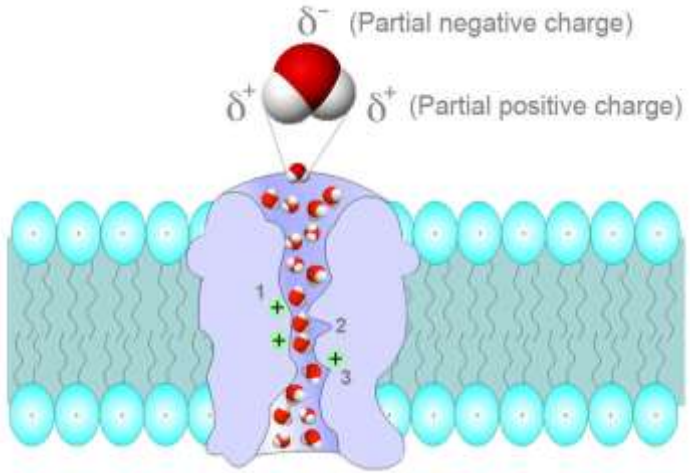

Figure 16: Aquaporins act as membrane-channel proteins that transport water or water plus glycerol

Aquaporins: Aquaporins are large family of major intrinsic proteins (MIPs) and have 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. In organisms water channels and osmoregulators can be substantial to survival and adaptability of these polyextremotolerant species in environment with low water activity $_{(aw)}$ (figure 16)[100,115].

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.[88]

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[29,88]. The level of adaptive capacity of a cell ultimately determines its destiny[88].

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 particular molecules that contribute 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 transmitting signals to the response of stress with high accuracy, these proteins include post-translational modification enzymes (such as, methylation, glycosylation, lipidation, 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 are as follows:

- ✓ In all organisms, signal transduction mechanisms are highly specific and highly sensitive and these properties are highly conserved during evolution[17].
- ✓ 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[60]
- ✓ 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[67,77].
- ✓ If the signal persists, receptor desensitization reduces or ends the response[96].
- ✓ Multicellular organisms have four general types of signaling mechanisms: GPCRs, Receptor enzymes, Gated ion channels and Intracellular receptors[51].
- ✓ Cells 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.

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[56,67,77,81].

As 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?. Studies 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 et al[4] 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.

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 significantly with accumulations of heat-shock proteins[4,86].

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[4,5].

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[1,67,77].

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[7,8]. Heat shock or chemical toxins that cause protein denaturation, activate the unfolded protein response (UPR) in the endoplasmic reticulum (ER) and mitochondria, hypoxia, respiratory poisons and xenobiotics that cause mitochondrial stress[83].

One of the problems 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 have. Generally, abiotic stress does not have positive effects on plant susceptibility to disease.[68,101]

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.[2,8]

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 the damage, caused by stress; 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.[10,15,68]

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.

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 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[63].

Because various cellular stress responses are closely related to multitude of common diseases, it is expected that having a better comprehension of background molecular mechanisms can enable us to intervene in 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[2,8,36,56,75].

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 had similar results in noxious outcomes and modified in disease level circumstances[8,75].

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.[28,35]

In humans, 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[53]. 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 are 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[71,87].

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

(129). As a relationship with CD73 and resistance to some anti-tumor therapies, as a link between CD73 and resistance to some anti-tumor therapies, combining anti-CD73 treatment of chemotherapy with immunotherapy can be a dramatic way for patients with high levels of CD73 expression[12,127,128]. In the future, while in the next age individual cancer treatment will begin, CD73 expression in cancer patients can also be an indicator of gene identification method (marker) in the selection and use of drugs that can be used to treat cancer[16,92,128].

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 an organism`s life and its relationship with its environment also seems to be inevitable for future studies[31]. Multi-omics approaches include genomics, transcriptomics, proteomics, metabolomics and phenomics help us to have comprehended integrated studies on animal, plants, microbes and their responses to external environment and produce multi-layered information that can answer what is going on in real-time within the cells under stress condition[31,76,92].

This acquired knowledge with using bioinformatics tools can be exploited for prediction and modeling of behavior the cell and interactions with environment under stressed condition within 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 or other organisms in extreme situation for bioremediation[25,92].

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References

1. Antonioli L., Yegutkin G.G., Pacher P., Blandizzi C. and Haskó G., Anti-CD73 in cancer immunotherapy: awakening new opportunities, *Trends in Cancer*, doi: 10.1016/j.trecan.2016.01.003, **2(2)**, 95-109 **(2016)**

2. Arnoldini M., Mostowy R., Bonhoeffer S. and Ackermann M., Evolution of stress response in the face of unreliable environmental signals, *PLoS Comput Biol*., https://doi.org/10.1371/journal.pcbi.1002627, **8(8)**, e1002627 **(2012)**

3. Azambuja J.H., Ludwig N., Braganhol E. and Whiteside T.L., Inhibition of the adenosinergic pathway in cancer rejuvenates innate and adaptive immunity, *International Journal of Molecular Sciences*, doi: 10.3390/ijms20225698, **20(22)**, 5698 **(2019)**

4. Antje Gerloff-Elias, Deepak Barua, Andreas Mölich and Elly Spijkerman, Temperature- and pH-dependent accumulation of heat-shock proteins in the acidophilic green alga Chlamydomonas acidophila, *FEMS Microbiology Ecolog.*, **56(3)**, 345–354 **(2006)**

5. King Allison M. and MacRae Thomas H., Insect Heat Shock Proteins During Stress and Diapause, *Annual Review of Entomology*, **60**, 59-75 **(2015)**

6. Nair Arathi, Chauhan Prashant, Saha Bhaskar and Katharina F., Conceptual Evolution of Cell Signaling, *Int J Mol Sci*., doi: 10.3390/ijms20133292, **20(13)**, 3292 **(2019)**

7. Aharon O., Bioenergetic aspects of halophilism, *Microbiology and Molecular Biology Reviews*: *MMBR*, **63(2)**, 334-48 **(1999)**

8. Alan Wells and Steven Wiley H., A Systems Perspective of Heterocellular Signaling, *Essays Biochem*., doi: 10.1042/EBC 20180015, **62(4)**, 607–617 **(2018)**

9. Butnariu M. and Samfira I., Aspects Relating of the Oxidative Stress to Living Organisms, *J Biodivers Endanger Species*, DOI: 10.4172/2332-2543.1000e106, **1**, e106 **(2013)**

10. Bateson Bateson P., Adaptability and evolution, *Interface Focus*, **7(5)**, 20160126 **(2017)**

11. Beavis P.A., Stagg J., Darcy P.K. and Smyth M.J., CD73: a potent suppressor of antitumor immune responses, *Trends in Immunology*, **33(5)**, 231-7 **(2012)**

12. Babazadeh R., Adiels C.B., Smedh M., Petelenz-Kurdziel E., Goksör M. and Hohmann S., Osmostress-induced cell volume loss delays yeast Hog1 signaling by limiting diffusion processes and by Hog1-specific effects, *PLoS One*, **8(11)**, e80901 **(2013)**

13. Burnstock G. and Di Virgilio F., Purinergic signalling and cancer, *Purinergic Signaling*, **9(4)**, 491-540 **(2013)**

14. Brigitta D., Bálint C. and Melinda E.T., Heat-Shock Proteins in Neuroinflammation, *Front Pharmacol*., doi: 10.3389/fphar.2019.00920, **10**, 920 **(2019)**

15. Cramer G.R., Urano K., Delrot S., Pezzotti M. and Shinozaki K., Effects of abiotic stress on plants: a systems biology perspective, *BMC Plant Biology*, doi: 10.1186/1471-2229-11-163, **11(1)**, 1-4 **(2011)**

16. Colgan S.P., Eltzschig H.K., Eckle T. and Thompson L.F., Physiological roles for ecto-5’-nucleotidase (CD73), *Purinergic Signaling*, doi: 10.1007/s11302-005-5302-5, **2(2)**, 351 **(2006)**

17. Chantranupong L., Wolfson R.L. and Sabatini D.M., Nutrient-sensing mechanisms across evolution, *Cell*, doi: 10.1016/j.cell.2015.02.041, **161(1)**, 67-83 **(2015)**

18. Dresselhaus T. and Hückelhoven R., Biotic, Biotic and Abiotic Stress Responses in Crop Plants (book), *Agronomy*, doi:10.3390/agronomy8110267, **8**, 267 **(2019)**

19. Jin D. et al, CD73 on tumor cells impairs antitumor T-cell responses: a novel mechanism of tumorinduced immune suppression, *Cancer Research*, **70(6)**, 2245–2255 **(2010)**

20. Delgado-Rizo V., Martínez-Guzmán M.A., Iñiguez-Gutierrez L., García-Orozco A., Alvarado-Navarro A. and Fafutis-Morris M., Neutrophil Extracellular Traps and Its Implications in Inflammation: An Overview, *Front Immunol*., doi: 10.3389/ fimmu.2017.00081, **8**, 81 **(2017)**

21. Daniel C. et al, Extracellular DNA traps in inflammation, injury and healing, *Nat Rev Nephrol*, https://doi.org/10.1038/s41581-019-0163-2, **15**, 559–575 **(2019)**

22. Di Virgilio F., Sarti A.C., Falzoni S., De Marchi E. and Adinolfi E., Extracellular ATP and P2 purinergic signalling in the tumour microenvironment, *Nature Reviews Cancer*, doi:10.1038/ s41568-018-0037-0, **18(10)**, 601-18 **(2018)**

23. Dietrich Averbeck, DNA Repair Mechanisms and Initiation in Carcinogenesis, *Comprehensive Toxicology*, https://doi.org/10. 1016/ B978-0-08-046884-6.01404-4, **14**, 49-62 **(2010)**

24. Duronio R.J. and Xiong Y., Signaling pathways that control cell proliferation, *Cold Spring Harbor Perspectives in Biology*, **5(3)**, a008904 **(2013)**

25. Debnath M., Pandey M. and Bisen P.S., An omics approach to understand the plant abiotic stress, *Omics: a Journal of Integrative Biology*, doi: 10.1089/omi.2010.0146, **15(11)**, 739-62 **(2011)**

26. Elmore S., Apoptosis: a review of programmed cell death, *Toxicologic Pathology*, doi: 10.1080/01926230701320337, **35(4)**, 495-516 **(2007)**

27. Escobar M.L., Echeverría O.M. and Vázquez-Nin G.H., Necrosis as programmed cell death, *In Cell Death-Autophagy, Apoptosis and Necrosis*, DOI: 10.5772/61483 **(2015)**

28. Flint A., Butcher J. and Stintzi A., Stress responses, adaptation and virulence of bacterial pathogens during host gastrointestinal colonization, *Virulence Mechanisms of Bacterial Pathogens*, **22**, 385-411 **(2016)**

29. Fulda S., Gorman A.M., Hori O. and Samali A., Cellular stress responses: cell survival and cell death, *International Journal of Cell Biology*, http://dx.doi.org/10.1155/2010/214074 **(2010)**

30. Fulda S., Gorman A.M., Hori O. and Samali A., Cellular stress responses: cell survival and cell death, *International Journal of Cell Biology*, https://doi.org/10.1155/2010/214074 **(2010)**

31. Pinu Farhana R., Beale David J., Paten Amy M, Konstantinos Kouremenos, Sanjay Swarup, Schirra Horst J. and Wishart David, Systems Biology and Multi-Omics Integration: Viewpoints from the Metabolomics Research Community, *Metabolites*, doi: 10.3390/metabo9040076, **9(4)**, 76 **(2019)**

32. Fain G.L., Matthews H.R., Cornwall M.C. and Koutalos Y., Adaptation in vertebrate photoreceptors, *Physiological Reviews*, **81(1),** 117-51 **(2001)**

33. Freeman B.C. and Beattie G.A., An overview of plant defenses against pathogens and herbivores, *The Plant Health Instructor*, DOI: 10.1094.PHI-I-2008-0226-01 **(2008)**

34. Gunde-Cimerman N., Plemenitaš A. and Oren A., Strategies of adaptation of microorganisms of the three domains of life to high salt concentrations, *FEMS Microbiology Reviews*, doi:10.1093/ femsre/fuy009, **42(3)**, 353-75 **(2018)**

35. Galluzzi L., Yamazaki T. and Kroemer G., Linking cellular stress responses to systemic homeostasis, *Nat Rev Mol Cell Biol*, https://doi.org/10.1038/s41580-018-0068-0, **19**, 731–745 **(2018)**

36. Grover A., Molecular biology of stress responses, *Cell Stress and Chaperones*, **7(1),** 1 **(2002)**

37. Gostinčar C., Ohm R.A., Kogej T., Sonjak S., Turk M., Zajc J., Zalar P., Grube M., Sun H., Han J. and Sharma A., Genome sequencing of four Aureobasidium pullulans varieties: biotechnological potential, stress tolerance and description of new species, *BMC Genomics*, **15(1)**, 549 **(2014)**

38. Gostinčar C., Stajich J.E., Zupančič J., Zalar P. and Gunde-Cimerman N., Genomic evidence for intraspecific hybridization in a clonal and extremely halotolerant yeast, *BMC Genomics*, doi:10.1186/s12864-018-4751-5, **19(1)**, 364 **(2018)**

39. Ghiringhelli F., Bruchard M., Chalmin F. and Rébé C., Production of adenosine by ectonucleotidases: a key factor in tumor immunoescape, *Journal of Biomedicine and Biotechnology*, 10.1155/2012/473712 **(2012)**

40. Guimarães-Costa A.B., Nascimento M.T., Wardini A.B., Pinto-da-Silva L.H. and Saraiva E.M., ETosis: A Microbicidal Mechanism beyond Cell Death, *Journal of Parasitology Research*, doi:10.1155/2012/929743**,** 929743 **(2012)**

41. Gostinčar C1., Lenassi M., Gunde-Cimerman N. and Plemenitaš A., Fungal adaptation to extremely high salt concentrations, *Adv Appl Microbiol*., doi: 10.1016/B978-0-12-387044-5.00003-0, **77**, 71-96 **(2011)**

42. Giglia-Mari G., Zotter A. and Vermeulen W., DNA damage response, *Cold Spring Harbor Perspectives in Biology*, doi: 10.1101/cshperspect.a000745, **3(1)**, a000745 **(2011)**

43. Gao Z.W., Wang H.P., Lin F., Wang X., Long M., Zhang H.Z. and Dong K., CD73 promotes proliferation and migration of human cervical cancer cells independent of its enzyme activity, *BMC Cancer*, doi: 10.1186/s12885-017-3128-5, **17(1)**, 1-8 **(2017)**

44. Farhad Hariri Akbari, Mansoor Omidi, Sepide Torabi, Seyed Mostafa Pirseyedi, Sayyed Sajjad Moravveji, Mehdi Shafiee Alavijeh, Baharak Behjat Sasan and Saeed Parvaneh, Efficient DNA extraction and purification protocol of medicinal plants which producing large amount of secondary metabolites, *J. Bio. Env. Sci*., **12(6)**, 67-78 **(2018)**

45. Hariri Akbari F., Omidi M., Torabi S., Bovard R., Shafiei M. and Safakish Kashani M.B., Applicable Fields of genetic engineering and biotechnology in Bioremediation and phytoremediation of heavy metals, *Journal of Biosafety Society*, **3(4),** https://scholar.google.com/scholar?oi=bibs&cluster=5905428646205799834&btnI=1&hl=en&authuser=1 **(2011)**

46. Hariri Akbari F., Omidi M., Torabi S., Khoshkharam M., Bovard R. and Shafiee M., Assessment of genetic diversity of iranian population of Anethum graveolens L.(dill) using AFLP molecular markers, *JBES*, **4(6)**, 141-152 **(2014)**

47. Hajtó T., Fodor K., Perjési P. and Németh P., Difficulties and perspectives of immunomodulatory therapy with mistletoe lectins and standardized mistletoe extracts in evidence-based medicine, *Evidence-Based Complementary and Alternative Medicine*, **11,** 1-6, DOI: 10.1093/ecam/nep191 **(2011)**

48. Eltzschig Holger K., Sitkovsky Michail V. and Robson Simon C., Purinergic Signaling during Inflammation, *N Engl J Med*., doi: 10.1056/NEJMra1205750, **367(24)**, 2322–2333 **(2012)**

49. Harfouche A., Meilan R. and Altman A., Molecular and physiological responses to abiotic stress in forest trees and their relevance to tree improvement, *Tree Physiology*, https://doi.org/10.1093/treephys/tpu012, **34(11)**, 1181-98 **(2014)**

50. He M., He C.Q. and Ding N.Z., Abiotic stresses: general defenses of land plants and chances for engineering multistress tolerance, *Frontiers in Plant Science*, https://doi.org/10.3389/fpls.2018. 01771, **9**, 1771 **(2018)**

51. Heldin C.H., Lu B., Evans R. and Gutkind J.S., Signals and Receptors, *Cold Spring Harb Perspect Biol*., doi: 10.1101/cshperspect. a005900, **8(4)**, a005900 **(2016)**

52. Isah T., Stress and defense responses in plant secondary metabolites production, *Biological Research*, doi: 10.1186/ s40659-019-0246-3, **52(1)**, 39 **(2019)**

53. Ischiropoulos H. and Beckman J.S., Oxidative stress and nitration in neurodegeneration: cause, effect, or association?, *The Journal of Clinical Investigation*, doi:10.1172/JCI17638, **111(2)**, 163-9 **(2003)**

54. Julien O. and Wells J.A., Caspases and their substrates, *Cell Death and Differentiation*, doi:10.1038/cdd.2017.44, **24(8)**, 1380-9 **(2017)**

55. Jordan J.D., Landau E.M. and Iyengar R., Signaling networks: the origins of cellular multitasking, *Cell*, doi: 10.1016/s0092-8674(00)00112-4, **103(2)**, 193-200 **(2000)**

56. Knight K. et al, Stress: from cells to ecosystems, Published by The Company of Biologists Ltd, *The Journal of Experimental Biology*, doi:10.1242/jeb.100727, **217**, 1-4 **(2014)**.

57. Kang H.M. et al, Ubiquitination of MAP1LC3B by pVHL is associated with autophagy and cell death in renal cell carcinoma, *Cell Death Dis*, doi:10.1038/s41419-019-1520-6, **10,** 279 **(2019)**

58. Kinclova-Zimmermannova L., Gaskova D. and Sychrova H., The Na+,K+/H+-antiporter Nha1 influences the plasma membrane potential of Saccharomyces cerevisiae, *FEMS Yeast Research*, **6(5)**, 792–800 **(2006)**

59. Konte T., Terpitz U. and Plemenitaš A., Reconstruction of the High-Osmolarity Glycerol (HOG) Signaling Pathway from the Halophilic Fungus Wallemia ichthyophaga in Saccharomyces cerevisiae, *Front. Microbiol*., doi: 10.3389/fmicb.2016.00901, **7**, 901 **(2016)**

60. Atkinson Nicky J. and Urwin Peter E., The interaction of plant biotic and abiotic stresses: from genes to the field, *Journal of Experimental Botany*, https://doi.org/10.1093/jxb/ers100, **63(10)**, 3523–3543 **(2012)**

61. Kholodenko B.N., Cell-signalling dynamics in time and space, *Nat Rev Mol Cell Biol*., doi: 10.1038/nrm1838, **7(3)**, 165-76 **(2006)**

62. Li J. and Yuan J., Caspases in apoptosis and beyond, *Oncogene*, doi:10.1038/onc.2008.297, **48,** 6194-206 **(2008)**

63. Lee J., Jo D.G., Park D., Chung H.Y. and Mattson M.P., Adaptive cellular stress pathways as therapeutic targets of dietary phytochemicals: focus on the nervous system, *Pharmacological Reviews*, doi:10.1124/pr.113.007757, **66(3)**, 815-68 **(2014)**

64. Loi S., Pommey S., Haibe-Kains B., Beavis P.A., Darcy P.K., Smyth M.J. and Stagg J., CD73 promotes anthracycline resistance and poor prognosis in triple negative breast cancer, Proceedings of the National Academy of Sciences, 11091-6 **(2013)**

65. Lu X.X., Chen Y.T., Feng B., Mao X.B., Yu B. and Chu X.Y., Expression and clinical significance of CD73 and hypoxia-inducible factor-1α in gastric carcinoma, *WJG*, **19(12)**, 1912 **(2013)**

66. Loi S., Pommey S., Haibe-Kains B., Beavis P.A., Darcy P.K., Smyth M.J. and Stagg J., CD73 promotes anthracycline resistance and poor prognosis in triple negative breast cancer, Proceedings of the National Academy of Sciences, 11091-6 **(2013)**

67. Lodish H., Berk A., Kaiser C.A., Krieger M., Scott M.P., Bretscher A., Ploegh H. and Matsudaira P., Molecular cell biology, Macmillan (book) **(2016)**

68. Meena K.K., Sorty A.M., Bitla U.M., Choudhary K., Gupta P., Pareek A., Singh D.P., Prabha R., Sahu P.K., Gupta V.K. and Singh H.B., Abiotic stress responses and microbe-mediated mitigation in plants: the omics strategies, *Frontiers in Plant Science*, doi: 10.3389/fpls.2017.00172, **9(8)**, 172 **(2017)**

69. Malmstrom C., Ecologists Study the Interactions of Organisms and Their Environment, *Nat Edu. Knowledge*, **3,** 88 **(2010)**

70. Mou Y. et al, Ferroptosis, a new form of cell death: opportunities and challenges in cancer, *J Hematol Oncol*, doi:10.1186/s13045-019-0720-y, **12(1)**, 34 **(2019)**

71. Musgrove R.E., Helwig M., Bae E.J., Aboutalebi H., Lee S.J., Ulusoy A. and Di Monte D.A., Oxidative stress in vagal neurons promotes parkinsonian pathology and intercellular α-synuclein transfer, *The Journal of Clinical Investigation*, DOI: 10.1172/JCI127330, **129(9) (2019)**

72. Mesa Miguel Antonio and Gloria Vasquez, "NETosis," *Autoimmune Diseases*, doi:10.1155/2013/651497, 651497 **(2013)**

73. Müller P. and Schier A.F., Extracellular movement of signaling molecules, *Developmental Cell*, **21(1),** 145-58 **(2011)**

74. Morkunas I., Woźniak A., Mai V.C., Rucińska-Sobkowiak R. and Jeandet P., The role of heavy metals in plant response to biotic stress, *Molecules*, doi: 10.3390/molecules23092320, **23(9)**, 2320 **(2018)**

75. Mariotti A., The effects of chronic stress on health: new insights into the molecular mechanisms of brain–body communication, *Future Science OA*, **1(3),** DOI: 10.4155/ FSO.15.21 **(2015)**

76. Muthamilarasan M., Singh N.K. and Prasad M., Multi-omics approaches for strategic improvement of stress tolerance in underutilized crop species: A climate change perspective, *In Advances in Genetics*, doi: 10.1016/bs.adgen.2019.01.001, **103,** 1-38 **(2019)**

77. Nelson D.L., Lehninger A.L. and Cox M.M., Lehninger principles of biochemistry (book), Macmillan **(2017)**

78. Nejat N. and Mantri N., Plant immune system: crosstalk between responses to biotic and abiotic stresses the missing link in understanding plant defence, *Signal*, **2**, O2 **(2017)**

79. Nowsheen S. and Yang E.S., The intersection between DNA damage response and cell death pathways, *Experimental Oncology*, **34(3)**, 243 **(2012)**

80. Norman L., Biddington, *Plant Growth Regul*, https://doi.org/10.1007/BF00025193, **4**, 103 **(1986)**

81. Newton A.C., Bootman M.D. and Scott J.D., Second Messengers, *Cold Spring Harb Perspect Biol*., doi: 10.1101/cshperspect. a005926, **8(8)**, a005926 **(2016)**

82. Nasr S., Mohammadimehr M., Vaghei M.G., Amoozegar M.A. and Fazeli S.A., Aureobasidium mangrovei sp. nov., an ascomycetous species recovered from Hara protected forests in the Persian Gulf, Iran, *Antonie Van Leeuwenhoek*, **111(9)**, 1697-705 **(2018)**

83. Oslowski C.M. and Urano F., Measuring ER stress and the unfolded protein response using mammalian tissue culture system, *In Methods in Enzymology*, **490**, 71-92 **(2011)**

84. Oren A., Probing saltern brines with an oxygen electrode: what can we learn about the community metabolism in hypersaline systems?, *Life*, **6(2)**, 23 **(2016)**

85. Otrin L., Kleineberg C., Caire da Silva L., Landfester K., Ivanov I., Wang M., Bednarz C., Sundmacher K. and Vidaković-Koch T., Artificial organelles for energy regeneration, *Advanced Biosystems*, **3(6)**, 1800323 **(2019)**

86. Xiong L., Schumaker K.S. and Zhu J.K., Cell signaling during cold, drought and salt stress, *The Plant Cell*, **14(suppl 1)**, S165-83 **(2002)**

87. Oren A., Life at high salt concentrations, *The Prokaryotes*, https://doi.org/10.1007/978-3-642-30123-0_57, **3**, 263-82 **(2006)**

88. Poljšak B. and Milisav I., Clinical implications of cellular stress responses, *Bosnian Journal of Basic Medical Sciences*, **12(2)**, 122 **(2012)**

89. Plemenitaš A., Lenassi M., Konte T., Kejžar A., Zajc J., Gostinčar C. and Gunde-Cimerman N., Adaptation to high salt concentrations in halotolerant/halophilic fungi: a molecular perspective, *Frontiers in Microbiology*, doi: 10.3389/fmicb.2014. 00199, **5**, 199 **(2014)**

90. Piro G., Carbone C., Carbognin L., Pilotto S., Ciccarese C., Iacovelli R., Milella M., Bria E. and Tortora G., Revising PTEN in the era of immunotherapy: new perspectives for an old story, *Cancers*, doi: 10.3390/cancers11101525, **11(10)**, 1525 **(2019)**

91. Péter G. and Rosa C., eds., Biodiversity and ecophysiology of yeasts, Springer-Verlag Berlin Heidelberg, doi:10.1007/3-540-30985-3_20 **(2006)**

92. Quezada C., Garrido W., Oyarzún C., Fernández K., Segura R., Melo R., Casanello P., Sobrevia L. and San Martín R., 5′-ectonucleotidase mediates multiple-drug resistance in glioblastoma multiforme cells, *Journal of Cellular Physiology*, **228(3),** 602-8 **(2013)**

93. Rogers K., Stress PSYCHOLOGY AND BIOLOGY: The Editors of Encyclopaedia Britannica, https://www.britannica.com/science/stress-psychology-and-biology **(2019)**

94. Ren W., Liu N., Yang Y., Yang Q., Chen C. and Gao Q., The sensor proteins BcSho1 and BcSln1 are involved in, though not essential to, vegetative differentiation, pathogenicity and osmotic stress tolerance in Botrytis cinereal, *Frontiers in Microbiology*, doi: 10.3389/fmicb.2019.00328, **10**, 328 **(2019)**

95. Reza B., Reza N.M., Mansoor O., Sepide T., Shamsali R., Farhad H.A., Mehdi S.A., Baharak B.S., Saeed P., Bagher S.K., The study of genetic diversity in different plant populations of Artemisia Annua L. native to northern Iran by molecular marker AFLP, *JBES*, **9(2)**, 51-9 **(2016)**

96. Rajagopal S. and Shenoy S.K., GPCR desensitization: Acute and prolonged phases, *Cell Signal*, doi: 10.1016/j.cellsig.2017. 01.024, **41**, 9-16 **(2018)**

97. Reggiori F., Komatsu M., Finley K. and Simonsen A., Autophagy: more than a nonselective pathway, *International Journal of Cell Biology*, doi: 10.1155/2012/219625 **(2012)**

98. Ren Z.H., Lin C.Z., Cao W., Yang R., Lu W., Liu Z.Q., Chen Y.M., Yang X., Tian Z., Wang L.Z. and Li J., CD73 is associated with poor prognosis in HNSCC, *Oncotarget*, doi: 10.18632/oncotarget, **7(38)**, 61690 **(2016)**

99. Rachel Abbotts et al, Role of DNA Repair in Carcinogenesis and Cancer Therapeutics, Encyclopedia of Cancer, Third Edition, https://doi.org/10.1016/B978-0-12-801238-3.65170-X, 363-385 **(2019)**

100. Rambow J., Wu B., Rönfeldt D. and Beitz E., Aquaporins with anion/monocarboxylate permeability: mechanisms, relevance for pathogen–host interactions, *Frontiers in Pharmacology*, doi: 10.3389/fphar.2014.00199, **5**, 199 **(2014)**

101. Ramegowda V. and Senthil-Kumar M., The interactive effects of simultaneous biotic and abiotic stresses on plants: mechanistic understanding from drought and pathogen combination, *Journal of Plant Physiology*, https://doi.org/10.1016/j.jplph.2014.11.008, **176**, 47-54 **(2015)**

102. Rejeb I.B., Pastor V. and Mauch-Mani B., Plant Responses to Simultaneous Biotic and Abiotic Stress: Molecular Mechanisms, doi: 10.3390/plants3040458, *Plants (Basel)*, **3(4)**, 458-75 **(2014)**

103. Rastogi R.P.1, Richa Kumar A., Tyagi M.B. and Sinha R.P., Molecular Mechanisms of Ultraviolet Radiation-Induced DNA Damage and Repair, *J Nucleic Acids*, doi: 10.4061/2010/592980, **2010**, 592980 **(2010)**

104. Rastogi R.P., Kumar A., Tyagi M.B. and Sinha R.P., Molecular mechanisms of ultraviolet radiation-induced DNA damage and repair, *Journal of Nucleic Acids*, doi: 10.4061/2010/592980 **(2010)**

105. Stephen P. et al, Abiotic and biotic stresses induce a core transcriptome response in rice, Cohen S.P. and Leach J.E., Abiotic and biotic stresses induce a core transcriptome response in rice, *Scientific Reports*, https://www.nature.com/articles/s41598-019-42731-8, **9(1)**, 1-1 **(2019)**

106. Samali A., Apoptosis: a mapped path to cell death, *Journal of Cellular and Molecular Medicine*, doi: 10.1111/j.1582-4934.2007.00165.x, **11(6)**, 1212 **(2007)**

107. Sato M., Kusumi R., Hamashima S., Kobayashi S., Sasaki S., Komiyama Y., Izumikawa T., Conrad M., Bannai S. and Sato H., The ferroptosis inducer erastin irreversibly inhibits system xc− and synergizes with cisplatin to increase cisplatin's cytotoxicity in cancer cells, *Scientific Reports*, **8(1)**, 1-9 **(2018)**

108. Slyskova J., Langie S.A., Collins A.R. and Vodicka P., Functional evaluation of DNA repair in human biopsies and their relation to other cellular biomarkers, *Frontiers in Genetics*, https://doi.org/10.3389/fgene.2014.00116, **5**, 116 **(2014)**

109. Shen F., Tang X., Cheng W., Wang Y., Wang C., Shi X., An Y., Zhang Q., Liu M., Liu B. and Yu L., Fosfomycin enhances phagocyte-mediated killing of Staphylococcus aureus by extracellular traps and reactive oxygen species, *Scientific Reports*, **6**, 19262 **(2016)**

110. Schneider E., Rissiek A., Winzer R., Puig B., Rissiek B., Haag F., Mittrücker H.W., Magnus T. and Tolosa E., Generation and Function of Non-cell-bound CD73 in Inflammation, *Front. Immunol.*, doi: 10.3389/fimmu.2019.01729, **10**, 1729 **(2019)**

111. Sannino S. and Brodsky J.L., Targeting protein quality control pathways in breast cancer, *BMC Biol*, https://doi.org/10.1186/s12915-017-0449-4, **15**, 109 **(2017)**

112. Sadej R. and Skladanowski A.C., Dual, enzymatic and non-enzymatic, function of ecto-5'-nucleotidase (eN, CD73) in migration and invasion of A375 melanoma cells, *Acta Biochimica Polonica*, **59(4)**, 647-652 **(2012)**

113. Saito H. and Posas F., Response to hyperosmotic stress, *Genetics*, https://doi.org/10.1534/genetics.112.140863, **192(2)**, 289-318 **(2012)**

114. Schneiderman N., Ironson G. and Siegel S.D., Stress and health: psychological, behavioral and biological determinants, *Annu Rev Clin Psychol*., doi: 10.1146/annurev.clinpsy.1.102803, 144141, **1**, 607-28 **(2005)**

115. Turk M. and Gostinčar C., Glycerol metabolism genes in Aureobasidium pullulans and Aureobasidium subglaciale, *Fungal Biology*, **122(1)**, 63-73 **(2018)**

116. Toscano S., Trivellini A., Cocetta G., Bulgari R., Francini A., Romano D. and Ferrante A., Effect of pre-harvest abiotic stresses on the accumulation of bioactive compounds in horticultural produce, *Frontiers in Plant Science*, https://doi.org/10.3389/fpls.2019.01212, **10**, 1212 **(2019)**

117. Tiwari V. and Wilson III D.M., DNA damage and associated DNA repair defects in disease and premature aging, *The American Journal of Human Genetics*, https://doi.org/10.1016/j.ajhg.2019.06.005, **105(2)**, 237-57 **(2019)**

118. Valdespino-Gómez V.M., Valdespino-Castillo P.M. and Valdespino-Castillo V.E., Interacción de las vías de señalización intracelulares participantes en la proliferación celular: potencial blanco de intervencionismo terapéutico [Cell signaling pathways interaction in cellular proliferation: Potential target for therapeutic interventionism], *Cir Cir*., doi:10.1016/j.circir.2015.04.015, **83(2)**, 165-174 **(2015)**

119. Wu Y., Song J., Wang Y., Wang X., Culmsee C. and Zhu C., The potential role of ferroptosis in neonatal brain injury, *Frontiers in Neuroscience*, **13**, 115 **(2019)**

120. Wettstein M.S., Buser L., Hermanns T., Roudnicky F., Eberli D., Baumeister P., Sulser T., Wild P. and Poyet C., CD73 predicts favorable prognosis in patients with nonmuscle-invasive urothelial bladder cancer, *Disease Markers*, doi: 10.1155/2015/785461 **(2015)**

121. Wang H., Lee S., Nigro C.L., Lattanzio L., Merlano M., Monteverde M., Matin R., Purdie K., Mladkova N., Bergamaschi D. and Harwood C., NT5E (CD73) is epigenetically regulated in malignant melanoma and associated with metastatic site specificity, *British Journal of Cancer*, **106(8)**, 1446-52 **(2012)**

122. Weinisch L., Kühner S., Roth R., Grimm M., Roth T., Netz D.J., Pierik A.J. and Filker S., Identification of osmoadaptive strategies in the halophile, heterotrophic ciliate Schmidingerothrix salinarum, *PLoS Biology*, **16(1)**, e2003892 **(2018)**

123. Zalar P., Gostinčar C., De Hoog G.S., Uršič V., Sudhadham M. and Gunde-Cimerman N., Redefinition of *Aureobasidium pullulans* and its varieties, *Studies in Mycology*, doi:10.3114/sim.2008.61.02, **61**, 21-38 **(2008)**

124. Zajc J., Kogej T., Galinski E.A., Ramos J. and Gunde-Cimerman N., Osmoadaptation Strategy of the Most Halophilic Fungus, Wallemia ichthyophaga, Growing Optimally at Salinities above 15% NaCl, *Applied and Environmental Microbiology*, https://doi.org/10.1128/AEM.02702-13, **80(1)**, 247–256 **(2014)**

125. Zhang B., CD73: a novel target for cancer immunotherapy, *Cancer Research*, doi: 10.1158/0008-5472.CAN-10-1544, **70(16)**, 6407-11 **(2010)**

126. Zhang B., CD73: a novel target for cancer immunotherapy, *Cancer Research*, doi: 10.1158/0008-5472.CAN-10-1544, **70(16)**, 6407-11 **(2010)**

127. Zhaowei Gao, Dong Ke and Zhang Hui-Zhong, The roles of CD73 in cancer, *BioMed Research International*, 10.1155/2014/460654, 460654 **(2014)**

128. Zhang B., CD73: a novel target for cancer immunotherapy, *Cancer Research*, **70(16)**, 6407-11 **(2010)**

129. Zhao-wei G., Dong K. and Hui-zhong Z., The Roles of CD73 in Cancer, *BioMed Research International*, doi: 10.1155/2014/460654 **(2014)**

130. Zhang L., Li J. and Xu W., A review of the role of Puma, Noxa and Bim in the tumorigenesis, therapy and drug resistance of chronic lymphocytic leukemia, *Cancer Gene. Ther*, **20**, 1–7 doi:10.1038/cgt.2012.84 **(2013)**

131. Hanahan D. and Weinberg R.A., The hallmarks of cancer, *Cell*, **100(1)**, 57-70 **(2000)**.

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