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Environmental Stress, Food Safety, and Global Health: Biochemical, Genetic and Epigenetic Perspectives

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Abstract

Environmental stress adversely affects the living organisms. To cope with the deleterious effects of the stresses, organisms have developed tolerance mechanisms which vary from individual to individual. Hence, the stress may be more deleterious for one individual in a particular situation but it may not be deleterious for the others. Environmental stresses trigger enhanced production of reactive oxygen species (ROS), causing an oxidative stress in the organism. Several antioxidants are generated inside the body to maintain optimum level of ROS in the body, and to protect cellular macromolecules from the damages caused by ROS. Excessive ROS production has been correlated with chronic diseases in human beings. Several phytochemicals are produced by plants for protection from the stresses, many of which are equally protective for animals also. The changing climatic conditions not only affect the productivity of crops and animals but the quality of produce is also affected. Advances in the fields of health and nutrition are resulting in the emergence of newer branch of science called nutrigenomics/nutriepigenomics which deals with the application of genomics to assess nutritional requirements of the individual. Growing evidence suggests that DNA methylation, chromatin modifications, and siRNA are involved in epigenetic regulation of genes under environmental stresses. Epigenetic changes have been associated with inactivation/activation of genes influenced by various abiotic and biotic stresses, resulting in the adaptation of an organism to the environment. In human, DNA demethylation of long interspersed nuclear elements has been identified as a useful epimark for early detection of cancer, which may also help in the epigenetic treatment of cancer. Genome editing techniques (like CRISPR-dCas9) may help dissecting the cause and effect of epigenomics variations associated with human diseases. However, further studies would be required to understand the molecular mechanisms of stress tolerance to deal with the stress-associated problems.

Keywords: Food safety; Global health; Environmental stress; Epigenetics; Nutriepigenomics

Introduction

Environmental stresses, such as extremes of temperature, water, salts etc., adversely affect biological activities in living organisms by disrupting cellular homeostasis [1]. Environmental factors are exceedingly complex in affecting biological activities, and the stress factors may interact with each other to worsen the condition. They adversely affect an organism in many ways. When the effects outweigh the ability of an individual to cope with the deleterious effects of the stress, the individual is considered under stress. Their detrimental effects on an organism may be apparent at relatively higher or lower level, depending on the individual. In fact, some of them may cause beneficial (priming) effect at the intermediate level of intensity of the stress [2]. It is also important to note that an environmental factor may be stressful for one individual in a particular situation, but it may not have deleterious effects on others. Thus, the effects of environmental stress depend on the interaction between genome and the environment [3].

Global climate change affects productivity and quality of produce, thus creates issues for food safety and health. Acclimatization and evolutionary mechanisms enable the organisms to withstand recurrent stresses. A better understanding of biochemical, genetic and epigenetic aspects of stress tolerance may help solving the problems of food security and healthy life. Human health is adversely affected by abiotic stresses. Adequate nutritious diet is essential for good health; however, nutritional requirement vary from organism to organism, and conditions to conditions under which the organism survive [4]. Hence, newer branches of science like nutrigenomics and nutriepigenomics are emerging rapidly and getting importance for managing healthy life. While nutrigenomics is the study of the effects of food constituents on gene expression, nutriepigenomics study the effects of food nutrients on human health through epigenetic changes. Evidence suggests that nutritional imbalance during gestation and lactation may cause non-communicable diseases like obesity, cardiovascular disease, diabetes, hypertension, and cancer. Thus, comprehensive studies on biochemistry, genetic and epigenetics of food producing and consuming organisms have become essential for global health in the 21st century and beyond.

Environmental Stress and Endurance of Organisms

Environmental stresses influence plant growth, and adversely affect the structural, developmental, physiological and biochemical processes of the organism. Drastic changes in environmental factors not only affect biological activities but also trigger enhanced production of reactive oxygen species (ROS), which create another stressful condition known as oxidative stress. The oxidative stress arises because of imbalance between production/accumulation of ROS and their detoxification in cells/tissues. Plants have developed innate systems to scavenge/detoxify ROS. The ROS can adversely affect cellular macromolecules such as cell-membrane, lipids, proteins, lipoproteins, and DNA. For example, excessive hydroxyl radical ($OH^•$) can cause lipid-peroxidation, damages to cell membranes and lipoproteins. Proteins and DNA may be damaged by the oxidative stress, causing loss of enzymatic activity and epigenetic changes in the genes. Interplay between ROS and epigenetics has attracted scientific interest with respect to autoimmune disease and mitophagy that has become of critical concern to chronic diseases [5]. Therefore, oxidative stress has been negatively correlated with survivability and longevity, and positively correlated with aging in animal [6]. Polyamines (e.g. putrescine, spermidine and spermine), the low molecular weight polycationic aliphatic molecules, are well-known to have anti-senescence and anti-stress effects due to their antioxidant properties. Spermidine is known to be involved in the protection of DNA from oxidative stress by quenching free radicals arising from ROS metabolism [7]. Studies have confirmed that many diseases including Alzheimer's disease, arthritis, cancer, cardiovascular diseases, cataract, diabetes, and Parkinson's disease, are correlated with excessive ROS production in the body and cellular redox imbalance [8]. Several antioxidants, both enzymatic and non-enzymatic, are generated inside the body [9] or consumed through food [8], which help to maintain the ROS at an optimum level in the body.

Food Safety and Global Health

Food is one of the unavoidable commodities for living organisms, and human being has always been interested in search and research on food items. Global population is likely to reach 9 billion by 2050, which would require increasing the food production by 70% over the next 35 years [10]. Unfortunately, the increasing global population, urbanization, and industrialization are not only decreasing the area under cultivation, and thus food production, but also increase the intensity of environmental stresses. To feed the burgeoning population, we need to produce more food and feed from the continuously decreasing per capita arable land, water, and other natural resources [10]. Providing ample food to the global populations is the primary task; a major challenge would be to produce it in a safe and sustainable manner [11]. The global climate is changing rapidly, which not only affects the productivity of the crops and animals but also adversely affects the quality of produce [4]. Investigations on stress responses of plants have been the focus of plant scientists for a long time, but newer insights in stress perception and signaling has been complemented by the growing evidence for stress-induced biochemical, physiological and epigenetic changes [12]. In spite of deploying several tolerance mechanisms, elite, high-yielding varieties often fail to survive under recurrent environmental stresses. A better understanding of genetic and epigenetic aspects of stress tolerance will not only be helpful in the development of transgenic plants for multiple-stresses, but also in stabilizing expression of the genes over the generations. Therefore, unraveling the mechanisms of stress tolerance and the underlying complex pathways has become essential [9].

Human health is adversely affected by climate changes due to the variations in weather conditions and the induced changes in human physiology. In human, environmental variation-induced changes in the components of epigenetics have been linked with the onset of health problems like autism, depression, schizophrenia, immune diseases, cardiovascular disease, cancer, diabetes, and obesity [13]. Food is a basic need of living organisms, and nutritious diet is essential for the maintenance of good health. However, it is essential to take basic nutrients in a balanced and bioavailable form. A balanced diet is supposed to contain all of the essential nutrients in the appropriate quantity needed for the growth, development, and maintenance of body [4]. Several phytochemicals are synthesized by plants for protecting themselves from environmental stresses, particularly insect pests and diseases. Since plants cannot move away to protect themselves from environmental stresses, they have evolved to produce a variety of protective compounds. Many a time, these phytochemicals are found to be equally protective for animals, albeit against different environmental stresses [4].

A larger part of food and feed comes from plants; hence, we need to study the biochemistry of plant. This would not only help in the formulation of balanced diets but also in other areas like pharmaceutical industry. Epidemiological data show that bioactive phytochemicals play important role in preventing and managing several human diseases like Alzheimer's diseases, cancer, cardiovascular diseases, and diabetes [14]. However, health benefits of a particular food/component are still researchable issues. Moreover, effective and efficient regulatory networks would be required to ensure safe-production and delivery of food items to the consumers.

Biochemistry and Genetics for Health-Security

Food is essential for survival and good health of animal. The global climate change is resulting in adverse environmental conditions for living organisms which affect their productivity. We not only need sufficient food to fill the stomach of burgeoning global population but also need to produce nutritious foods for healthy populations. This is where phytochemistry can play important role in producing healthy-food [4]. A balanced diet in sufficient amounts is equally important. A larger part of our food, particularly vegetarian diet, comes from plants; hence, we need to study phytochemistry of plant parts. The major group of phytochemicals currently being studied is the secondary metabolites of plants. These phytochemicals are synthesized in plants mainly to protect them from invaders and adverse environmental conditions. Scientific and technological advances in the fields of health and nutrition are resulting in the emergence of newer branch of sciences namely nutrigenomics and nuriepigenomics which involve the application of genomic/epigenomic information to assess nutritional requirements for a healthy life of an individual under given environmental conditions. While nutrigenomics/ nutriepigenomics is a promising branch of science, research in this area is still in the preliminary stages and it may take several years to prescribe an accurate and effective diet for an individual [4].

Since domestication of plants, considerable progress has been made in agriculture driven by the behavioral/social changes in human beings [3]. Domestication of plants followed by selection of elite genotypes, breeding varieties for higher yield, better food quality, and nutrition, tolerance to abiotic and biotic stresses, and the concurrent technological advancements have enabled a considerable increase in food grain production. Plants, being sessile in nature, are constantly challenged by environmental stresses; hence, they have adopted biochemical, molecular and epigenetic strategies to cope up with the environmental stresses [15]. Growing evidence suggests that DNA methylation, chromatin modifications, and siRNA are involved in epigenetic regulation of genes under environmental stresses [16]. Epigenetic mechanisms have been implicated in the regulation of stress-associated genes [17]. Many a time, environmental stress fluctuates so rapidly that no other regulatory mechanism can appropriately control expression of the gene in an efficient manner [3]. Living organisms do possess readers, writers and erasers of epigenetic marks [18]. These epigenetic factors can be deployed for epigenetic engineering of an individual for incorporating desirable changes and making it tolerant to environmental stresses. However, it would be essential to understand the epigenetic state of the donor to ensure proper re-establishment of the epigenetic state in the recipient for expression of the gene(s) [19]. Today, scientists can isolate any gene of interest from any organism and incorporate it into a small self-replicating extra-chromosomal genetic element for multiplication and expression of the gene. The recombinant DNA molecule, thus produced, can be introduced into host cells of our choice. These have empowered scientists to tailor-make genes and have they expressed in a living organism to produce the desired product [20].

Genetic/Epigenetic Engineering for Sustainable Food Production

Genetic engineering promises to contribute significantly to agriculture, energy and health sectors, and environmental stewardship as well. Biotechnology enables gene transfer by overcoming the natural barriers, thus creating a universal gene pool. It has been successfully used to develop insect/pest/herbicide-resistant crop plants, hasten animal growth, enhanced productivity, improved animal health and several new animal/plant products. In the health industry, genetic engineering is being used to produce more efficient vaccines, antibiotics and other therapeutics in a cost-effective manner. Molecular markers, DNA profiling are successfully used to diagnose hereditary diseases and to predict the chance of an individual inheriting a disease from the affected parent(s). Through gene therapy, scientists are targeting to cure genetic diseases by replacing defective genes with healthy ones. Hence, molecular biology and biotechnological tools and techniques, if properly integrated with other technologies, provide tremendous opportunities for sustainable developments in several areas of human endeavours [21].

In the last few decades, genetic engineering research has resulted in the development and release of several genetically modified organisms (GMOs) for commercial uses [22]. GMOs may also have direct or indirect effects on the environment including gene-flow to wild relatives, pest resistance, and other unintended effects. However, a most significant environmental benefit of genetically modified (GM) crops is the drastic reduction in pesticide application in agriculture. GM technology offers the development of an entirely new system of pest management having several advantages over conventional biological control agents, but fewer of the drawbacks. Plant-incorporated protectants (e.g. *Bt* gene) have been one of the modern crop biotechnology applications with several products in the world market. Use of *Bt* genes may be considered as the beginning of new and safer technologies to bring about sustainable agriculture towards protecting the environment. Bt Cry proteins are specifically active against species of the orders Lepidoptera (Moth and butterflies), Diptera (Flies and Mosquitoes), and Coleoptera (Beetles and Weevils). Several Bt proteins (Cry3, Cry6A, Vip, Sip, and others from different strains of *Bacillus thuringiensis*) have been identified to be effective against Coleopteran insects [23,24].

The global area of transgenic crops has been increasing rapidly [25], in spite of a multitude of public and scientific concerns about the environmental and food safety issues of GM crops. One of the issues of concern of GM technology pertains to the inclusion of superfluous and undesirable DNA sequences, as a consequence of the plant transformation protocols being used. In case of microprojectile-mediated DNA transfer, the vector backbone sequences of the plasmid get integrated into the host genome along with the transgene(s) [26]. The integrated vector sequences may serve as recombination hotspots leading to illegitimate recombination and transgene rearrangement. Besides, there are possibilities of new replicons, comprising of plasmid ori and host plant genomic DNA, to escape into the environment. Silencing of transgenes has been a major commercial risk hampering the economic exploitation of transgenic plants, which may be addressed through epigenetics of transgene integration. With the increasing number of countries adopting molecular tools and techniques in their life science research and development activities, the biosafety issues are gaining importance to ensure biological safety for the public and the environment [20]. Unfortunately, biosafety and biosecurity regulations are still weaker in many countries and lack the proper infrastructure for their implementation. Genetic engineering promises to improve the quality of human life if used judiciously. Contrary to this, if used haphazardly and carelessly, it might have negative impacts on the environment [22].

Epigenetics of Stress Tolerance and Human Health

Epigenetics refers to the studies of heritable changes in gene expression due to modifications in DNA bases and in the associated chromatin proteins without any change in the underlying nucleotide sequence [12]. Epigenetic modifications have been associated with spatial/temporal activation and inactivation of genes in response to various abiotic and biotic factors, resulting in better adaptation of the organism to the environment. Environmental stresses cause epigenetic alterations, many of which are not permanent (do not cause genetic change) yet affect gene expression, and some of them may be heritable also as stress memory [19]. Epigenetic changes are also being reported to be involved in regulation of gene expression during the development, tissue differentiation, and suppression of transposable elements (TEs) in plants and animals [27]. Analysis of the stress-associated genes and their regulation under the stress are continuously being utilized to improve our understanding about the ability of an organism to adapt to changing climatic conditions. Nucleotide sequence of DNA is responsible for carrying genetic information in most of the living organisms. However, cytosine and adenine residues can be chemically modified by the addition of epigenetic information to the genetic material. Methylation of promoter and gene-body play important roles in the regulation of gene expression. Similarly, variation in chromatin structure also plays important role in stress tolerance. The chromatin consists of histone proteins, in addition to DNA bases, which results in a variety of possible modifications of amino acid residues making the histone protein the main source of complexity in the epigenome. Although more than 150 epigenomic features are known so far, experimental studies usually concentrate on a few of them only. The most commonly profiled epigenetic marks with respect to regulation of gene expression include methylation of cytosine and adenine in DNA, acetylation of lysine, methylation of arginine and lysine, phosphorylation of serine and threonine, and mono- or polyubiquitylation of lysine [28,29]. Though epigenetic base modification and histone modifications are reversible in nature, cross-talk between cytosine methylation and histone modifications make the epigenetic codes more complex.

In human, demethylation of long interspersed nuclear elements (LINE) has been identified as a useful epimark for early detection of cancer. Methylation status of several genes provides an indication to many types of cancer. For example, hypomethylation of *cytochrome P450 1B1, p-Cadherin, p53, BAGE* and *maspin* genes have been related

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to prostate cancer, invasive breast cancer, lung cancer, ovarian and breast cancer, and colorectal and thyroid cancer, respectively [30]. Epigenetic changes particularly because of xenobiotic content of food and environmental pollutions (Figure 1) are reported to be involved in the repression of anti-aging genes that are associated with chronic disease epidemic [31]. Unhealthy foods have been reported to repress *Sirtuin 1* gene involved in epigenetic modification and inactivate immune system [5]. Environmental stresses repress *Sirtuin 1* with the induction of heat shock proteins. *Sirtuin 1* levels can be determined and used to reverse/prevent mitochondrial apoptosis and programmed cell death in chronic diseases [32].

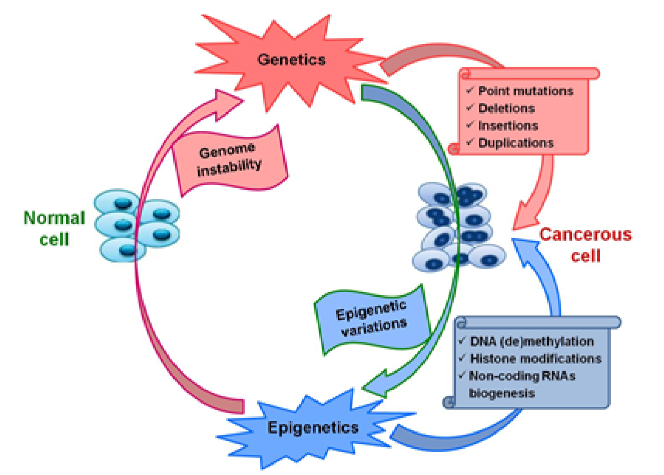

Figure 1: Genetic and epigenetic perspectives of cell division under the changing environmental conditions in animal system.

Methylcytosine (5-mC) has been reported to be involved in regulation of many important biological processes, including movement of transposable elements (TEs), genome imprinting and regulation of stress-responsive gene expression [33]. Cytosine methylation can further reinforce histone modification patterns conducive to gene expression. Some of the histone modifications such as acetylation, phosphorylation, and ubiquitination have been reported to increase gene transcription, while biotinylation and SUMOylation have been reported to suppress gene expression. The dynamic histone modification may get converted into relatively more stable DNA methylation [34]. Environmentally induced epigenetic changes have been linked to a variety of pathologies, and epigenetics-based therapy is an emerging area of research and shows amazing perspectives. Suppression of the genes associated with tumorigenesis by histone acetylation has been reported. Azacitidine and histone deacetylase (HDAC) inhibitors are promising agents in clinical trials for patients diagnosed with cancer. The U.S. Food and Drug Administration have approved two different types of drugs for the epigenetic treatment of cancer. DNA methylation inhibitors (azacitidine and decitabine) and histone deacetylase inhibitors (vorinostat, sodium phenylbutyrate, entinostat and panobinostat) are some of the commonly used chemicals in epigenetic therapy of cancer [35]. Increased epigenetic changes have been reported at the initiation of a tumor, which continues to grow with the advancement in the stage of cancer. Epigenetics of invasion, metastasis, and epithelial-mesenchymal transformation events might provide a novel way for the treatment of breast cancer [36]. Combining these epigenetic agents for activation of tumor suppressor genes with synergistic *in vitro* anti-neoplastic activity provides a promising approach in the cancer chemotherapy [29].

Recent advances have facilitated genome-wide examination of epigenetic modifications in the context of disease phenotypes. Analogous to genome-wide association studies (GWASs), epigenome-wide association studies (EWASs) enable comprehensive analysis of epigenomic marks in cohorts of patients and control groups in the context of the disease phenotypes. Hypermethylation of the promoter region of genes related to cancer provides a tool for cancer diagnosis. Most of the studies have been concentrated on DNA methylation; however, the first histone modifications based EWAS has been published recently [37]. EWASs have generated thousands of epigenomic markers associated with diseases, but causes of the disease-associated epigenetic changes remain largely unclear. Clustered regularly interspaced short palindromic repeats (CRISPR)-dCas9 based approach might help to dissect the cause and effect of epigenomics variations associated with human diseases.

Conclusions and Future Perspectives

Epigenetics is an emerging field of study; however it is still in the infancy stage. Hypermethylation of cancer causing gene, particularly the promoter region, provides a tool for the development of biomarkers towards early detection of tumors and drug designing for its treatment. Inhibitor of DNA methylation (e.g. Azacitidine) has been found to reactivate and cancer-related genes, and it is being used in clinical trials for treating cancer patients. Similarly, considerable variations in epigenetic phenotypes in plants have been recognized over the last two decades. Growing evidence suggests that epigenetic mechanisms contribute to stress responses in plants and animals. It is proposed that epigenetic machinery plays more dynamic roles in plants which are having relatively more repetitive elements in gene-rich euchromatic regions. Epialleles emerge at a higher frequency, far exceeding the rate of mutations; hence, give rise to new alleles. Heritable epialleles are considered as a newer source of polymorphism, and they might have significant implications in plant breeding. Stressful conditions result in hypermethylation of DNA, and the stress-induced methylation suppresses genome activity which could be at the core of better performance of the hybrids.

Epigenetic modulation of parental imprinting may lead to the development of superior endosperm in seed crops. A better understanding of the epigenetic mechanisms of seed development will eventually reveal the mysteries of apomictic seed development in plants. Epigenetic manipulation of heterosis and apomixis in commercial crops might help to maintain hybrid vigor indefinitely, thus overcoming the current limitations of plant breeding in maintaining hybrid vigor over the generations. With a better understanding of the epigenetic mechanism of transgene silencing, it would be possible to maximize the advantages of transgenic technology. The recent developments in ultra-high-throughput techniques have revolutionized identification of epigenetic marks and improving our knowledge of epigenetics. However, further studies need to be focused on unraveling the coordination among the known epigenetic marks, their biological significance and evolutionary roles. Since epigenetic states are metastable and vary in response to environmental signals, a deeper understanding of the molecular mechanisms of epigenetics would allow us to deal with several diseases [38].

Epigenetic manipulation through CRISPR-dCas9 may not only help in epigenome engineering in a great variety of cell types and organisms for food safety but also for improved health. Besides engineering dCas9, sgRNA can be modified to recruit effector proteins to a targeted genomic region. This approach not only allows recruitment of different epigenetic modifiers to the same locus but also increases the number of modifiers that can be recruited per dCas9:sgRNA complex [39,40]. However, other challenges would be to define the correct position and number of sgRNAs required for the desired effects. Considerable efforts are being made to understand the aberrant methylation of DNA and the pathways involved in such deviations. Such efforts might pave the ways for prognosis and treatment of cancer in animals and development of stress tolerant crop plants.

The views expressed herein are those of the author only. These may not necessarily be the views of the institution/organization the author is associated with.

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