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Applying hormesis in aging research and therapy

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A paradigm shift is occurring in biogerontology. After decades of systematic collection of data describing age-related changes in organisms, organs, tissues, cells and macromolecules, it has become clear that there are no universal patterns of aging and age-related alterations. The range and diversity encountered in the progression of aging phenotype shows that aging is: (1) different in different species; (2) different in different individuals within a species; (3) different in different organs, systems and tissues within an individual; (4) different in different cells within an organ; (5) different in different organelles within a cell; and (6) different in different macromolecules.[1,2] These observations have challenged biogerontologists to reconsider their strategies for understanding aging and for developing efficient ways to prevent age-related impairments and diseases.

Causes of aging

Most of the researchers involved in aging research now hold the view that unlike development, which is a highly programmed and well-coordinated process in the life history of an organism, aging is stochastic and nondeterministic.[3,4] Aging is an emergent phenomenon manifested in protected environments and occurs mainly as a result of the failure of homeostasis.[5] Furthermore, the evolutionary theories strongly argue against the existence of genes that may have evolved specifically to cause aging and to determine maximum lifespan of an organism.[6] The genetic regulation of lifespan is primarily in terms of determining what can be called as the essential lifespan (ELS) of a species.[1,2] ELS is defined as the time required to fulfill the Darwinian purpose of life, that is successful reproduction and continuation of generations. For example, species undergoing fast maturation and early onset of reproduction with large reproductive potential generally have a short ELS. In contrast, slow maturation, late onset of reproduction, and small reproductive potential of a species is concurrent with its long ELS.

The genes that do influence longevity are those that have evolved in accordance with the life history of a species for assuring ELS. Such genes are termed longevity assurance genes[7] or gerontogenes[8] for their effects on aging, and are considered to constitute various maintenance and repair pathways, including antioxidative defenses, DNA repair, fidelity of genetic information transfer, and stress response pathways. There are several examples of genes, particularly in DNA repair and antioxidant pathways, whose activities have been reported to correlate directly with species lifespan. Further evidence that the maintenance and repair pathways are the main determinants of longevity comes from experiments performed to retard aging and to increase the lifespan of organisms.

Until now, several putative gerontogenes have been reported for various aging systems, including yeast, nematodes, insects and mammals. The molecular identities of some of these genes have been established. In the case of the budding yeast, the nematode, and the fruit fly these genes are longevity-determining genes, but the molecular pathways affected by them have little or no similarity among different organisms. For example, in *Saccharomyces cerevisiae*, the functions of LAG, RAS, uth and Sir complex range from being transmembrane proteins to transcriptional silencing of telomeres.[7,9–14] In the fungus *Podospora anserina*, a gerontogene *grisea* codes for a putative copper-activated transcription activator.[15] In *Caenorhabditis elegans*, the normal functions of various gerontogenes include PI3-kinase activity, tyrosine kinase receptor activity, transcription factor activity and insulin receptor-like activity, and it is only when mutated that a loss or alteration in the activity of their gene products is associated with increased longevity.[16–20] In *Drosophila*, the *methuselah* (*mth*) gene, whose predicted protein sequence has homology to several GTP-binding protein coupled receptors, is

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also associated with increased lifespan and enhanced resistance to various forms of stress.[21] Similarly, a mutation in the gene encoding an adapter protein $p66^{shc}$, which is involved in the oxidative stress response, extends the life span of mice.[22] In the case of the mouse *klotho* gene, which is a membrane protein β-glucosidase,[23] and the human Werner's gene, which is a DNA helicase,[24] the phenotype of premature aging is manifested along with a plethora of diseases. Additionally, genetic linkage studies for longevity in mice have identified major histocompatibility complex (MHC) regions,[25] and quantitative trait loci (QTL) on chromosomes 7, 10, 11, 12, 16, 18, 19[26,27] as putative gerontogenes. In human centenarians, certain alleles of HLA locus on chromosome 6, different alleles of APO-E and APO-B, and DD genotype of angiotensin converting enzyme (ACE) have been linked to their long life span.[25,28,29]

The diversity of the genes associated with aging and longevity of different organisms indicates that whereas the genes involved in repair and maintenance pathways may be important from an evolutionary point of view (the so-called "public" genes), each species may also have additional "private" gerontogenic pathways that influence its aging phenotype.[30]

Homeodynamics

It has been suggested that age-related alterations observed at all levels of organization are a sign of *continuous remodeling* of the body,[31,32] against the ill effects of progressively failing repair and maintenance processes. In this context, Hayflick has correctly pointed out that *a more revealing question that is rarely posed is why do we live as long as we do*?[4] The answer to such a question lies in the basic property of homeostasis, which is a characteristic of all living systems. Traditionally, homeostasis is defined as the maintenance of a constant internal state for the efficient functioning and the performance of the organism. Recently, convincing arguments have been put forward to replace the term homeostasis with *homeodynamics*, taking into account the dynamic nature of living processes in an ever-changing lifeline.[33]

A critical component of the homeodynamic property of living systems is their capacity to respond to stress. In this context, the term "stress" is defined as a signal generated by any physical, chemical or biological factor (stressor), which in a living system initiates a series of events in order to counteract, adapt and survive (Table 1). Often these mechanisms are common to several stresses as well as different species, and have been given a collective term "the general-adaptive syndrome".[34] Aging, however, is characterized by a decrease in the adaptive abilities due to progressive failure of maintenance.[6,35,36]

Table 1 Examples of stress responses at various levels of organization

Biological level	*Response*
Organismic	Avoidance by behavioral adjustments
Physiological	Thermoregulation, immune system, hormonal alterations
Organ	Detoxification, blood circulation, respiration rate
Tissue	Regeneration
Cellular	Cell proliferation, apoptosis
Molecular	DNA repair, heat shock response, protein degradation, free radical scavenging

Hormesis in aging

Although the phenomenon of hormesis has been defined variously in different contexts,[37,38] hormesis in aging is characterized by the beneficial effects resulting from the cellular responses to mild repeated stress.[1,2,39–41] It is not the aim of this article to provide a comprehensive list of studies that have demonstrated the anti-aging and life-prolonging effects of a wide variety of stresses, for which several other articles are available.[39–45] Stresses that have been reported to delay aging and prolong longevity include temperature shock, irradiation (UV, gamma and X-rays), heavy metals, pro-oxidants, alcohols, exercise and calorie restriction. However, almost none of these studies were undertaken with a conscious effort to test the hypothesis of hormesis. Mostly, it is in retrospect that the same authors or others reviewing the published data have interpreted their results as evidences for hormesis. Independent of these studies related to aging and longevity, significant efforts have been made to successfully develop a reliable scientific database for the phenomenon of hormesis in a wide range of biological situations, including its evolutionary significance.[38,46–50]

The idea of applying hormesis in aging research and therapy is based in the fact that one of the immediate cellular responses to external and internal stress is the upregulation of maintenance and repair pathways. Therefore, it has been suggested that adopting the approach of hormesis to stimulate the biochemical pathways of maintenance and repair can be a promising strategy for understanding the gerontogenic pathways of aging, for slowing down aging and for preventing the onset of age-related diseases.[1,51–53]

Whereas in case of severe stress upregulation may become energetically so costly that the biological system is overwhelmed and collapses completely, mild stress can be stimulatory without becoming too costly and thus have positive hormetic effects. Furthermore, it may be possible to use the approach of hormesis in order to identify genes that are important for aging and longevity. For example, if repeated mild heat shock treatment has life-prolonging and anti-aging effects in cells and organisms, it is likely that the genetic pathways of heat shock response are also associated with longevity determination. Similarly, other chemical, physical and biological treatments can be used to unravel various pathways of maintenance and repair whose sustained activities improve the physiological performance and survival of cells and organisms.

This will be helpful not only for having a complete understanding of the mechanistic aspects of the aging process, but also for preventing the onset of various age-related diseases by maintaining the efficiency of repair processes. The clinical implications of the hormesis-like stress response in the diagnosis and treatment of several diseases including arthritis, Duchenne muscular dystrophy, multiple sclerosis, myocardial ischemia, mitochondrial encephalomyopathy, some cancers, and autoimmune diseases, such as systemic lupus erythematosis are being increasingly realized.[54] Some of the main targets for prevention of age-related pathology include the following biochemical processes that may be accessible to modulation through hormesis. These are: (1) an appearance and accumulation of abnormal proteins and proteolytic products leading to, for example, Alzheimer's disease; (2) posttranslational modifications and cross-links between macromolecules, leading to, for example, cataracts and atherosclerosis; (3) reactive oxygen species-induced mitochondrial defects leading to, for example, Parkinson's disease, Huntington's disease, and amyotropic lateral sclerosis; and (4) genomic instability leading to, for example, cancers.

Issues to be resolved

Although at present there are only a few studies performed that utilize mild stress as a modulator of aging and longevity, hormesis can be a useful experimental approach in biogerontology. However, there are several issues that remain to be resolved before mild stress can be used as a tool to modulate aging and prevent the onset of age-related impairments and pathologies. Some of the main issues are:

1. establishing biochemical and molecular criteria for determining the hormetic levels for different stresses;
2. identifying differences and similarities in stress response pathways initiated by different stressors;
3. quantifying the extent of various stress responses;
4. determining the interactive and pleiotropic effects of various stress response pathways
5. adjusting the levels of mild stress for age-related changes in the sensitivity to stress;
6. determining the biological and evolutionary costs of repeated exposure to stress; and
7. determining the biological significance of relatively small hormetic effects, which may or may not have large beneficial effects during the entire lifespan.

Only a wide-ranging and open discussion on these and related questions can resolve these issues. Such a resolution is necessary in order to develop objective tests for application and utilization of the powerful approach of hormesis in biomedical and health-related issues.

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