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Homeostasis, homeodynamics, and aging

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I. Concepts and terms

All living systems, in contrast to the non-living systems, have the intrinsic ability to respond, to counteract and to adapt to the external and internal sources of disturbance. The traditional conceptual model to describe this property is *homeostasis*, which has dominated biology, physiology and medicine since 1930s. However, tremendous advances made in our understanding of the processes of biological growth, development, maturation, reproduction, and finally, of aging, senescence and death have led to the realization that homeostasis model as an explanation is seriously incomplete. The main reason for the incompleteness of the

homeostasis model is its defining principle of "stability through constancy", which does not take into account the new themes, such as cybernetics, control theory, catastrophe theory, chaos theory, information and interaction networks, that comprise and underline the modern biology of complexity.

Since 1990s, the term *homeodynamics,* introduced by F. E. Yates in 1994, is being increasingly used – though it has not yet fully succeeded in replacing homeostasis. The concept of homeodynamics accounts for the fact that the internal milieu of complex biological systems is not permanently fixed, is not at equilibrium, and is a dynamic regulation and interaction among various levels of organization.

Almost in parallel with the development of the concept of homeodynamics, another term *allostasis*, coined and introduced by Peter Sterling and J. Eyer in 1988, has also been gaining recognition and use. According to the allostasis model, "stability through change" is the most realistic situation for living biological systems. Allostasis model also takes into account the characteristics such as reciprocal trade-offs between various cells, tissues and organs, accommodative sensing and prediction with respect to the severity of a potential stressor, and the final cost of making a response and readjustment to bring about the necessary change. Every act of allostasis adds to the *allostatic load* in terms of, for example, unrepaired molecular damage, reduced energy deposits and progressively less efficient or less stable structural and functional components. Aging, senescence and death are the final manifestations of unsuccessful homeodynamics or failure of allostasis.

II. Components of the homeodynamic machinery

Of the numerous biochemical and physiological pathways and processes operating in cells, tissues, organs and systems in any organisms, the key pathways and processes which can be

considered to be quintessential components of the homeodynamic machinery are the following:

1. The multiple pathways of nuclear and mitochondrial DNA repair, including those for maintaining the accuracy of the information transfer from DNA to RNA to proteins, and those for the removal of spontaneous lesions in DNA.
2. The processes for sensing and responding to intra- and extra-cellular stressors, such as heat shock response, hemeoxygenase response, stress hormones, and ionic fluxes.
3. The pathways for protein repair, such as the renaturation of proteins by chaperones, and the enzymic reversal of the oxidisation of amino acids.
4. The pathways for the removal and turnover of defective proteins by proteasomes and lysosomes.
5. The antioxidative and enzymic defences against reactive oxygen species.
6. The processes for the detoxification of harmful chemicals in the diet.
7. The cellular and humoral immune responses against pathogens and parasites, including massive apoptosis (programmed cell death) after the completion of the cellular immune response.
8. The processes of wound healing, blood clotting and tissue/organ regeneration.

In addition to the above main categories of pathways and processes comprising the homeodynamic machinery, some other physiological processes include the temperature control, the epigenetic stability of differentiated cells, and fat storage and energy utilization.

Of course, all these processes involve genes whose gene products and their interactions give rise to a "homeodynamic space", which is the ultimate determinant of an individual's chance and ability to survive and maintain a healthy state. At present, our knowledge about the number of genes and their variants, their multiple interactions and

consequences is too meagre to identify, define and manipulate the homeodynamic machinery in any sensible way. In the case of human beings and other social animals, determining the role of psychosocial factors as integral components of the homeodynamic machinery is one of the biggest challenges.

III. Homeodynamic space and longevity

Why do members of different species have different lifespans, and what determines the lifespan potential of an organism, are challenging evolutionary questions. The natural lifespan of a species has also been termed "essential lifespan" (ELS) by Suresh Rattan, or the "warranty period" of a species, by Bruce Carnes and S. Jay Olshansky. ELS is defined as the time required to fulfil the Darwinian purpose of life, that is successful reproduction for the continuation of generations. 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. For example, the ELS of *Drosophila* is less than a week as compared with the ELS of less than 50 years of *Homo sapiens*, even though in protected environments (laboratories and modern societies), a large proportion of populations of both species can and do live for much longer than that.

Since 1980s, Robin Holliday and Tom Kirkwood have been developing arguments based on the allocation of energy and metabolic resources (EMR) as the determinants of an organism's longevity and survival potential. According to their ideas, available EMR must be partitioned between three fundamental features of life: (1) the basic metabolism, which includes biochemical synthesis, respiration, cell turnover, movement, feeding, digestion and

excretion; (2) the reproduction; and (3) the maintenance through homeodynamic machinery as described above.

Whereas basic metabolism is essential for all animals, the extent of investment in reproduction and maintenance can vary between species. This is the trade-off, known as the disposable soma theory of aging, between investment in maintenance and investment in reproduction, which are related inversely. The evolved balance between the two depends on the life history strategy and ecological niche of the species. Several comparative studies have reported positive correlations between lifespan and the ability to repair DNA, detoxify reactive oxygen molecules, respond to and counteract stress, and replace worn-out cells. In addition, negative correlation has been demonstrated between longevity and the rate of damage accumulation, including mutations, epimutations, macromolecular oxidation and aggregation of metabolic byproducts.

Although the reasons for the longevity differences among the species can be explained by the disposable soma theory, significant differences among individuals within a species are much harder to explain. Genes, milieu (environment) and chance factors are thought to be the determinants of individual lifespan. Of these factors, some understanding is emerging with respect to the genes and their associations with survival and longevity. In human beings, association studies on gene polymorphism and longevity have identified numerous genes which function in a variety of biochemical pathways, such as cytokines, cholesterol metabolism, DNA repair and heat shock response. Such studies will ultimately lead to the elucidation of the nature and number of genes involved in comprising the homeodynamic space of an individual, which may be the basis for its modulation and intervention.

IV. Aging as the failure of homeodynamics

The evolved nature of the homeodynamic machinery, in accordance with the life history traits of different species, sets an intrinsic genetic limit on the ELS (essential lifespan) as described above. Therefore, aging is considered as an emergent phenomenon seen primarily in protected environments which allow survival beyond the natural lifespan in the wild. No real genes *for* aging (gerontogenes) are thought to exist, and the nature of genes in aging was defined by Suresh Rattan in 1995 as being "virtual" gerontogenes owing to their indirect effects on aging and longevity.

Based on a large body of descriptive data, gleaned during a period of more than fifty years in the field of biogerontology, Robin Holliday has defined aging as the progressive failure of homeodynamics. Collectively, biogerontological data characterize aging as a progressive accumulation of molecular damage in nucleic acids, proteins and lipids. Since the occurrence and accumulation of molecular damage is mainly stochastic, aging is manifested differently in different species, in individuals within a species, organs, tissues, cells and in subcellular-components within an individual. The main cause of age-related accumulation of molecular damage and its consequences is the inefficiency and failure of maintenance, repair and turnover pathways which constitute the genetically-determined homeodynamic machinery.

A generalised definition of aging as the failure of homeodynamics still requires mechanistic explanation(s) as to why such a failure occurs in the first place and what controls the rate of failure in different species. Over the last fifty years, researchers have proposed a large number of hypotheses which attempt to explain how the observed age-related changes in macromolecules, cells, tissues, organs and systems may occur. Main examples of such hypotheses include altered gene regulation, somatic mutation accumulation, protein errors and

modifications, reactive oxygen species and free radicals, immune-remodeling and neuroendocrine dysfunctioning. At the cellular level, the so-called telomere loss theory, and epimutation theory of progressive loss of DNA methylation are other examples of providing mechanistic explanations for the loss of proliferative potential of normal, differentiated and diploid cells *in vitro* and *in vivo*.

These and other related hypotheses which provide a variety of explanations for understanding the observed age-related alterations at a specific level can be quite useful within their area of focus. However, in order to answer the question why the occurrence of detrimental and eventually lethal changes cannot be avoided completely, one has to appeal to the evolutionary theories of ageing and longevity, as discussed above.

Several theoretical and mathematical models are being developed in order to understand the interactive nature of the biological networks and trade-offs. Recently, the reliability theory of aging and longevity proposed by Leonard Gavrilov, about the inevitable failure of complex systems such as cells and organisms has reiterated the principle that no process can be one-hundred-percent accurate one-hundred-percent of the time; and it is the interactive nature of genes, milieu and chance that effectively determines how long homeodynamic ability can keep a biological system alive.

V. Homeodynamics and aging intervention, prevention and therapies

According to the homeodynamics-based explanations for aging and longevity described above, having the bodies that we have developed after millions of years of evolution, occurrence of aging in the period beyond ELS, and the onset of one or more diseases before eventual death appear to be the "normal" sequence of events. This viewpoint makes modulation of aging different from the treatment of one or more specific diseases. In the case

of a disease, such as a cancer of any specific kind, its therapy will, ideally, mean the removal and elimination of the cancer cells and restoration of the affected organ/tissue to its original disease-free state. What will then be the "treatment" of aging and to what original "age-free" stage one would hope to be restored? Considering aging as a disease and then trying to cure that disease is unscientific and misguided. Similarly, although piecemeal replacement of non-functional or half-functional body parts with natural or synthetic parts made of more durable material may provide a temporary solution to the problems of age-related impairments, it does not modulate the underlying aging process as such.

Scientific and rational anti-aging strategies aim to slow down aging, to prevent and/or delay the physiological decline, and to regain lost functional abilities. Strengthening, improving or enlarging the homeodynamic space at the level of all genes comprising the homeodynamic machinery of an individual may be the ideal anti-aging solution. However, such a gene-therapy approach for gerontomodulation requires redesigning the blueprint for structural and functional units of the body at the level of genes, gene products, macromolecular interactions, molecular-milieu interactions, and so on. Considering how little information and knowledge we have at present about all those interacting variants of genes, molecules, milieu and chance, it is not clear what this approach really means in practical and achievable terms.

Improving the milieu in which the homeodynamic machinery operates is the other strategy that is being followed by most of the so-called anti-aging experts. Some of the main approaches include supplementation with hormones including growth hormone, dehydroepiandrosterone (DHEA), melatonin and estrogen, and nutritional supplementation with synthetic and natural antioxidants in purified form or in extracts prepared from plant and animal sources. Although some of these approaches have been shown to have some clinical

benefits in the treatment of some diseases in the elderly, none of these really modulate the aging process itself. Furthermore, claims for the benefits of intake of high doses of vitamins and various antioxidants and their supposed anti-ageing and life-prolonging effects have very little scientific evidence to back them.

In contrast to this, nutritional modulation through caloric restriction (CR) has been shown to be an effective anti-aging and longevity extending approach in rodents and monkeys, with possible applications to human beings. But, this is a highly debatable issue at present both in terms of the practicalities of defining CR and of applying CR in human beings in physiological and evolutionary contexts.

VI. Homeodynamics and hormesis as an aging modulator

In a more realistic and near-future scenario, a promising approach in aging intervention and prevention is based in making use of an organism's intrinsic homeodynamic property of self maintenance and repair. Since aging is characterized by a decrease in the adaptive abilities due to progressive failure of homeodynamics, it has been hypothesized that if cells and organisms are exposed to brief periods of stress so that their stress response-induced gene expression is upregulated and the related pathways of maintenance and repair are stimulated, one should observe anti-aging and longevity-promoting effects. Such a phenomenon in which stimulatory responses to low doses of otherwise harmful conditions improve health and enhance lifespan is known as *hormesis.*(Although the term hormesis was coined in the 1930s, its revival and wide use is accredited to Edward Calabrese, *see bibliography)*.

The phenomenon of hormesis has been defined variously in different contexts. For example in toxicology, pharmacology and radiation biology, hormesis is defined by a non-linear U-shaped or reverse-U-shaped dose response curves. In biogerontology, hormesis

is characterized by the beneficial effects resulting from the cellular responses to mild repeated stress that challenges and stimulates homeodynamic machinery. The paradigm of hormesis in aging is moderate exercise which is well known to have numerous beneficial effects despite or because of it being a generator of free radicals, acids, and other damaging effects.

Mild stresses that have been reported to delay ageing and prolong longevity in various systems (for example, yeast, *Drosophila,* nematodes, rodents and human cells) include temperature shock, irradiation (UV-, gamma- and X-rays), heavy metals, pro-oxidants, acetaldehyde, alcohols, hypergravity, exercise and food restrcition. Hormesis-like beneficial effects of chronic but mild undernutrition have been reported for human beings. Intermittent fasting has been reported to have beneficial effects on glucose metabolism and neuronal resistance to injury.

Although at present there are only a few studies performed which 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 by improving the homeodynamic space of an individual. Some of the issues in the applicability of hormesis as a homeodynamic stimulator are the following.

1. establishing biochemical and molecular criteria for determining the hormetic levels of 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.

Resolution of these issues requires much more research on hormesis than being carried out at present. The proof of the hormetic principle has now been provided by experiments with a wide variety of biological systems and by using a range of physical, chemical and biological stressors. Two of the main lifestyle interventions, exercise and reduced food intake, both of which bring their beneficial and anti-aging effects through hormesis, are being widely recognized and increasingly practiced as an effective means of achieving a healthy old age. In the consideration of irradiation as a hormetic agent, epidemiologic studies of the public, medical cohorts, and occupational workers confirm that low doses of radiation are associated with reduced mortality from all causes, decreased cancer mortality, and reduced mutation load observed in aging and cancer. Increasing use of low-dose total body irradiation as an immunotherapy for cancer also has its basis in hormesis. However, in order that this approach could be developed into a safe and preventive strategy against a variety of age-related diseases, certain issues, for example those related to radiation load versus mortality curve, by-stander effects, and trhe nature of energetic particles, need to be resolved.

Hormesis through mental challenge and through mind-concentrating meditational techniques may be useful in stimulating inter- and intra-cellular debris-removal processes, and thus preventing the neuronal loss that leads to the onset of age-related neurodegenerative diseases. One can also expect the availability of certain nutriceutical and pharmacological hormetic agents to mimic mild stress as a challenge for the homeodynamic machinery. Plant components such as resveratrol, celastrol and curcumin are among the potential hormetic molecules identified so far.

VII. Recapitulation

Living systems survive by virtue of a set of defensive maintenance and repair systems which comprise their homeodynamic ability. A large number of interacting genes and genetic networks constitute this machinery, the exact details of which are yet to be unravelled. Successful homeodynamics is crucial for the growth, development and maturation of an organism until the reproduction and continuation of generations is assured. Homeodynamics is thus a longevity assurance mechanism, whose strength, efficiency and range have evolved in accordance with the evolutionary history of the species. Survival beyond the required essential lifespan of a species is necessarily accompanied by the progressive accumulation of random molecular damage. The progressive failure of homeodynamics leads to the physiological malfunctioning manifested as a general functional decline, diseases and ultimate death. Rational strategies to slow down aging or to prevent the onset of age-related frailty and diseases require stimulating and strengthening the homeodynamics of individuals.

BIBLIOGRAPHY

Austad, S. N. (1997). Why We Age. New York, John Wiley & Sons, Inc.

Calabrese, E. J. (2002). Hormesis: changing view of the dose-response, a personal account of the history and current status. *Mutat. Res.* **511**: 181-189.

Calabrese, E. J. (2003). The maturing of hormesis as a credible dose-response model. *Nonlinear. Biol. Toxicol. Med.* **1**: 319-343.

Calabrese, E. J. (2005). Horemtic dose-repsonse relationship in immunology: occurrence, quantitative features of the dose response, mechanistic foundations, and clinical implications. *Crit. Rev. Toxicol.* **35**: 89-295.

Holliday, R. (1995). Understanding Ageing. Cambridge, UK., Cambridge University Press.

Holliday, R. (2000). Ageing research in the next century. *Biogerontology* **1**: 97-101.

Kirkwood, T. B. L. (1999). Time of Our Lives. London, Weidenfeld & Nicolson.

Olshansky, S. J. and B. A. Carnes (2001). The Quest for Immortality. New York, W. W. Norton & Co.

Rattan, S. I. S. (1995). Gerontogenes: real or virtual? *FASEB J.* **9**: 284-286.

Rattan, S. I. S., Ed. (2003). Modulating Aging and Longevity. Dordrecht, The Netherlands., Kluwer Academic Publ.

Rattan, S. I. S. (2004). Aging intervention, prevention, and therapy through hormesis. *J. Gerontol. Biol. Sci.* **59A**: 705-709.

Rattan, S. I. S., Ed. (2005). Aging Interventions and Therapies. Singapore, World Scientific Publishers.

Schulkin, J., Ed. (2004). Allostasis, homeostasis, and the costs of adaptation. Cambridge, UK., Cambridge University Press.

Yates, F. E. (1994). Order and complexity in dynamical systems: homeodynamics as a generalized mechanics for biology. *Math. Comput. Model.* **19**: 49-74.