Molecular basis of aging

edited by Alvaro Macieira-Coelho.

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TABLE OF CONTENTS

INTRODUCTION

Those without expertise in gerontology, but interested in understanding the investigations carried out to elucidate the mechanisms of aging, face many difficulties.

PROBLEMS ARISING FROM COMPARATIVE BIOLOGY AND PHYSIOPATHOLOGY

One difficulty comes from the tendency that many gerontologists have of looking for a global view of the mechanisms of aging along the evolutionary scale, extrapolating data, and then seeking for universal explanations. Comparative biology has shown that the mechanisms of aging cannot be universal.[1] This does not mean, however, that studies performed on lower organisms along the evolutionary scale are useless in understanding human aging. Some mechanisms may be conserved, but as an organism becomes more complex other regulatory mechanisms come into the picture, and as a result the homeostatic regulation of the life span also increases in complexity. Moreover, along the evolutionary road some mechanisms have remained preponderant in some species, while becoming secondary in others.

It is obvious that the mechanisms controlling the life span in *Drosophila*, for instance, where there is no cell turnover in the mature organism, cannot be the same as those in a mammal, where permanent renewal occurs throughout the life span in many cell compartments, and whose genome is more complex than that of a fly. Initial mortality rates are also extremely high in flies; as compared with humans, they are 1000 times higher.[1] This illustrates fundamental developmental differences, showing that the mechanisms regulating the life span in *Drosophila* cannot be extrapolated to vertebrates.

A disregard for comparative biology and physiopathology has led to shortcuts and misinterpretations that have retarded the advancement of gerontology and handicapped communications between gerontologists.

We have limited this volume to experimental approaches performed with mammals but even among mammals striking differences appear, indicating that extrapolations should be carried out with restraint.

Among mammals, rodents are the laboratory animals most often used in gerontology studies, and the data obtained are often extrapolated to humans in spite of fundamental biologic differences. It has been considered that "molecular genetics and cell biology reinforce the evidence that rats and men are basically similar, so that many of the laboratory findings on aging in rats are substantially valid for our own species."[2] However, at the molecular and cellular levels, specificities exist which have obvious implications for survival. For instance, human cells are capable of removing *Micrococcus luteus* UV-endonuclease-susceptible sites, as opposed to rat cells which almost completely lack this type of DNA repair.[3] It has been suggested that this characteristic may render rat cells more dependent on postreplication repair systems which are error prone.[3] This may lead to an increased frequency of genetic changes in rat cells.

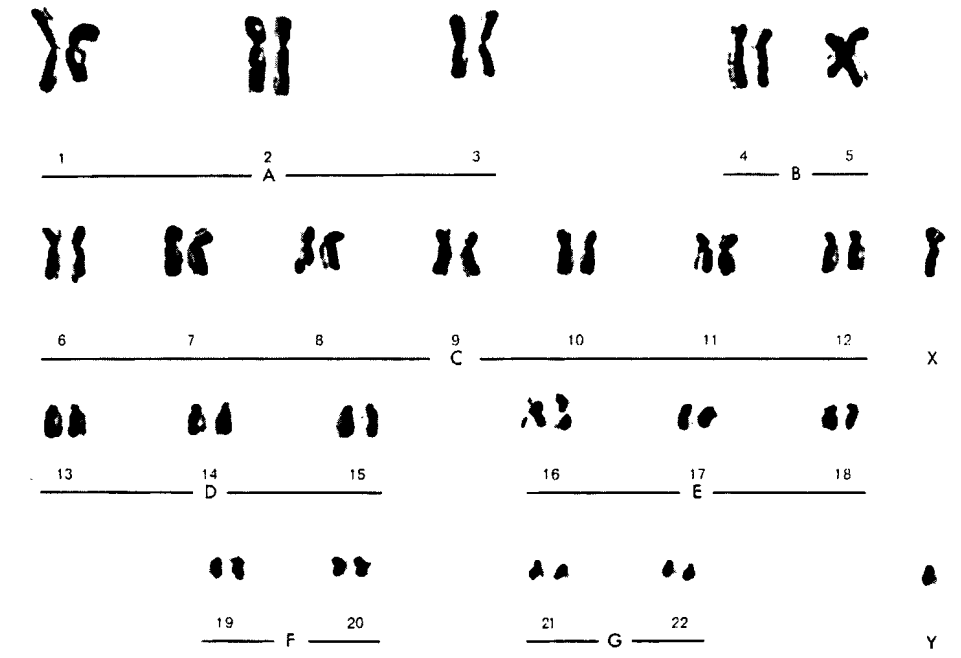
Another difference between the genetic material of rodents and humans became apparent in transfection experiments, which showed that a significantly lower number of sequences become stably incorporated by human cells as compared to hamster cells.[4] This shows that human cells are less prone to be modified by new information integrated from external sources.

Many experimental results on the biology of aging of mice have been thought to be applicable to humans. However, this is hardly conceivable when one considers the profound differences in the molecular and cellular biology of these two species. The DNA repair abilities of mouse cells differ from human cells and may be implicated in the cellular instability that characterizes this rodent group, expressed by the predisposition to malignant transformation. Mouse cells have a reduced capacity for excision repair as revealed by the low host-cell reactivation of UV-irradiated herpes simplex virus.[5,6] Single-strand break repair also differs; the relative increased efficiency of this type of repair is higher in human than in mouse fibroblasts.[7] Moreover, contrary to the situation in human cells, telomere shortening does not occur in mouse cells during aging.[8]

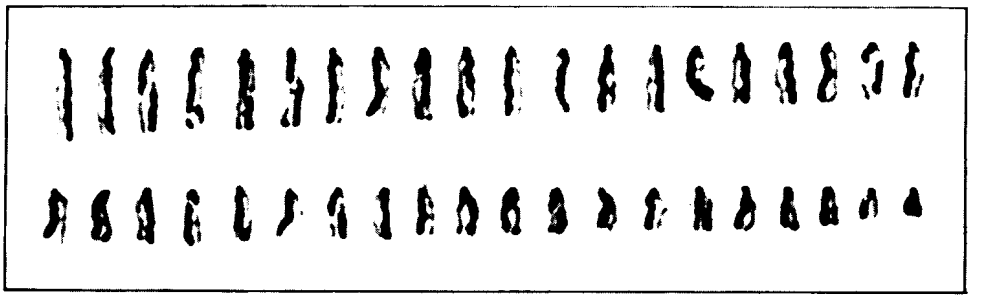
Furthermore, hybridization experiments between human and mouse cells revealed an incompatibility between the two genomes, making genetic interpretation of the transmission of interspecies phenotypic markers impossible.[9] These experiments showed that expression of the marker in the hybrid does not obey any law, even that of Mendelian genetics. These results have implications for certain experiments that are supposed to determine the presence of putative genes responsible for cell senescence.

Even the morphological comparison of mice and human chromosomes (Figure 1) highlights the fundamental differences existing in the organization of the two genomes. One can assume a different hierarchy within the centromere-telomere segment, implying specific regulatory constraints for each species.[10]

In addition to their particular morphology, mouse chromosomes display interesting features that could be responsible for some aspects of the



Human



Mouse

Figure 1
Human (top) and mouse (bottom) chromosomes. The cells were labeled with bromodeoxyuridine during two rounds of replication, then prepared for visualization of the karyotype. After fixation they were stained with Giemsa. The chromatid which incorporated the precursor in both DNA strands is stained dark, the one that incorporated only in one strand is lightly stained. A few exchanges between sister chromatids can be seen, although more frequently in the mouse chromosomes.

physiopathology of this rodent's life span; this is reviewed in detail in Chapter 1, dealing with the reorganization of the genome. Mouse chromosomes display a pronounced instability which is manifested as a high

probability of recombinational events.[11] This must be due to some yet-unknown structural organization of the mouse genome, and to the presence of molecules that regulate recombination. The efficiency of converting nicks into crossovers due to the transient appearance of a protein called R-protein, which facilitates DNA reannealing, seems to be greater in the mouse.[10]

This characteristic of the mouse genetic material seems to be responsible, at least in part, for the particularly high transformation frequency of mouse cells; it must also be responsible for the high frequency of mutable events of this species. This might be useful for the group's survival as it provides a greater capacity to adapt and evolve with environmental changes, but is deleterious to the individual because of the instability it creates at the molecular and cellular levels.

The "plasticity" of the genome, i.e., the potential for rearrangements, seems to play an essential role in development, aging, and disease; this is a feature that has been neglected in gerontology. A suitable potential for genome rearrangements must be important for differentiation to progress through development. Plasticity of the genome diminishes through development, maturity, and aging (see Chapter 1); this could be a control mechanism to avoid deviations from normal development that could lead to disease. Indeed, unregulated genome plasticity, such as the expansion of small repeats, can lead to disease. An increased potential for chromosomal recombinational events is also related to a predisposition for neoplastic transformation.[12]

The lack of plasticity seems to lead to deviations from normal development as is the case with Werner's syndrome patients. The cytogenetic studies of this disease have shown that it is characterized by rearrangements which become fixed.[13]

A puzzling feature, seemingly correlated to the plasticity of the genome and one that distinguishes the cells of mammalian species, has been observed during the *in vitro* cultivation of their fibroblasts. This feature is their relative propensity to overcome proliferative senescence and acquire the potential for unlimited proliferation. This has been one of the interesting windfalls of the aging of proliferative cells concept and of its opposite, cell immortalization;[14] it has implications for evolutionary differences between species that also have a bearing on cancer and aging *in vivo*.

Swim and Parker[15] had obtained data suggesting that cells from some species might be endowed with a limited number of doublings, while others were able to divide indefinitely. Later, it became apparent that the probability of escaping proliferative senescence, and of becoming immortalized, has a bearing on the susceptibility to be transformed by all types of carcinogens and oncogenes.[12,16] The failure to grasp this important conclusion led to the indiscriminate use of cells in the study of the effects

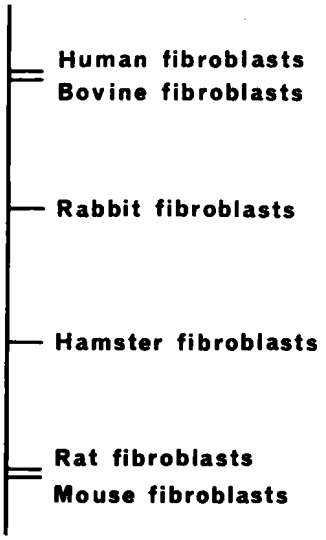


Figure 2
Scale indicating, from top to bottom, the increasing probability that fibroblasts from different species have of escaping proliferative senescence and immortalizing.

of carcinogens, and to incorrect interpretations of the action of oncogenes due to misunderstandings of the target cell biology. Indeed, when comparing fibroblasts from different species based on the probability of spontaneously yielding a population with unlimited growth potential, the resulting scale goes from very low to 100% probability (Figure 2). The latter occurs with rat and mouse fibroblasts regardless of the animal strain.[17] In general, murine fibroblasts tend to have a higher probability of yielding permanent cell lines than, for instance, their human and bovine counterparts. This led to the claim that one or two genes were necessary for the transformation of murine cells. In fact, these cells evolve spontaneously through the different transformation steps, and the introduction of those genes simply accelerates a latent potential.[12,16]

It is also easier to induce cancers in those species whose fibroblasts have a higher probability of escaping *in vitro* senescence. The species whose fibroblasts immortalize easily also seem to be more short lived. Is there a possible causality relationship between cell instability and a short life span? The question remains open but the relationship seems reasonable, especially with the realization that cellular instability seems to be related to the instability of the genome.[12,16] These fundamental molecular and cellular interspecies differences, expressed in their respective physiopathologies, have not been considered by gerontologists.

Other aspects of comparative physiopathology also illustrate the difficulty in extrapolating data from one species to another. Women, for instance, have a unique propensity for breast cancer (25% of all malignant tumors) as compared to other mammals. Breast cancer in dogs constitutes approximately 13%, in cats 5%, and in cattle and horses 1% of all cancers.[18] There are also marked differences in the pathology of atherosclerosis.

CONCLUSIONS FROM EXPERIMENTAL SYSTEMS SHOULD FIT THE PHYSIOLOGY OF ORGANISM AGING

Another difficulty for gerontology students comes from the incorrect utilization of certain experimental systems. This is particularly true for experiments attempting to elucidate the mechanisms that alter the proliferative potential of some cell compartments during aging of the organism. This has created a wall between cytogerontologists and the other gerontologists, through which communication is barely possible.

Both the investigators studying the proliferative potential of cells and the gerontologists working in other fields were misdirected, following claims that the decline of the proliferative potential of some somatic cells is due to an increase in the fraction of nondividing cells. Cloning of cells was first used to determine the cell fraction capable of division during the proliferative history of human fibroblast populations.[19] It concluded that "the increase in the fraction of nondividing cells is approximately exponential, as is the increase in the probability of death for certain privileged human populations." Other investigations, where ^{3}H-thymidine labeling of cells was used for the same purpose, claimed that "the data showed a continual decrease in the fraction of cells synthesizing DNA during aging."[20]

Both of these works reached a conclusion incompatible with the physiology of a mammalian organism, i.e., that cellular senescence is due to the increase of nondividing cells during serial population doublings. Surprisingly, this conclusion was accepted by most investigators using this experimental system; it led to the almost obsessive search for an evaluation of the number of nondividing cells, and for the stage of the division cycle where cell growth is arrested. Cells that had lost their division potential were called senescent cells, and cellular senescence was defined as the reproductive failure after a period of replication. Most works claiming to study cellular senescence still attempt to identify the events that occur when a cell population enters the final nondividing phase. Some investigations, claiming to have discovered inductors of cell senescence, were simply reporting on the way to make cells enter the postmitotic stage.

These types of interpretations also led to an association between the limited proliferation potential and apoptosis, for which there is no experimental evidence. In regard to senescence of proliferative cells, chromatin studies have shown that the terminal postmitotic cell is not in apoptosis.[21] At this time, apoptosis appears as a homeostatic mechanism of cell elimination and renewal, which might in fact protect the organism from cells that have completed their life span and from disorderly proliferations. When uncontrolled, it is also implicated in pathological states.

It is obvious that aging of the mammalian organism is not due to the loss of the division potential of proliferative cell compartments. The transition to a postmitotic phase is an interesting and important problem of

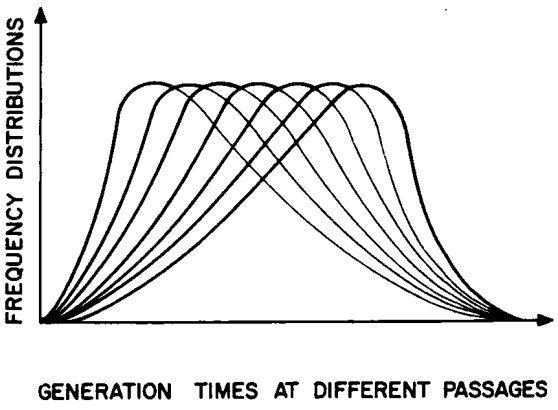


Figure 3
Shift to the right of the heterogeneity of generation times of human mesenchymal cells, summarized from the data obtained on the kinetics of proliferation during proliferative aging.[23-30] The shift in generation times is the expression of the functional drift.

cell biology, but there is no evidence whatsoever of its relevance to aging of the organism. Therefore, many gerontologists that used other experimental systems dismissed the one proposed by Hayflick,[22] claiming that it is irrelevant to the study of aging.

Meanwhile, other works gave a different view of aging of proliferative cells — one compatible with the physiology of aging of the organism. They showed that long before a cell population enters the final nondividing phase, progressive changes can be detected in the response to growth stimuli and in the way the cells transit through the cycle.[23-30] These works demonstrated the uncertainty and heterogeneity that are implicated in the probability of cycling, in contrast to the other data that assume an all-or-none event, obviously incompatible with the physiology of the organism.

Most investigators missed the point that the significance for aging of the experimental system proposed by Hayflick[22] is to have revealed how serial replication affects the coordination of the response to growth factors, and the way cells progress through the divison cycle rather than how cells are arrested when they become postmitotic. Furthermore, the ability to divide is just one function among others; if the response to growth stimuli and the way the cells transit through the cycle are progressively modified by serial divisions, then other functions are modified as well.

The commitment to divide depends on several factors such as the substratum for cell attachment, concentration of nutrients, growth factors and inhibitors, cooperation between cells, intracellular modifications, etc. As for aging of the organism, the relevance of modifications occurring through serial proliferation is the increased heterogeneity in the response of proliferative cell compartments to those different parameters; this shows the functional evolution of a cell compartment.

During the course of proliferation, cells progress through different functional stages so that their distribution among those stages is modified (Figure 3). This implicates new cell interactions and regulations and is an important component of the permanent evolution suffered by a mammalian organism through its life span. This occurs not only in several mitotic

cell systems,[31] but also in conditionally mitotic compartments such as hepatocytes.[32]

The implications that cellular changes occurring during proliferation have on aging of the organism are presented in detail in Chapter 1 concerning these cell compartments.

It should be stressed that the cellular changes taking place in mitotic cell populations can also be created by events independent from those occurring during the division cycle, such as pathological conditions or external events (e.g., action of the sun on the skin).[33]

There is growing evidence that favors the proposal in which the evolution of a fibroblast population through proliferation is a differentiation process.[34] The mesenchyme is known for its inductive properties on neighboring cells; however, the specific functions of the different phases traversed by its cells have not been ascertained. The function of the terminal fibroblastic cell has yet to be determined; until this is elucidated, the terminal differentiation hypothesis shall remain a hypothesis. In any case, one has to distinguish the life cycle of a cell population that is part of homeostasis from those changes due to and contributing to aging of the organism.

The terminal postmitotic fibroblast is present in the normal adult organism,[21] but its eventual role in the aging process has not been found. However, the terminal cell was found in increased amounts in aging-related pathological states;[21,35] the interesting possibilities this finding offers to distinguish between physiological and pathological aging are discussed in Chapter 1. Since this volume deals mainly with aging per se, and not with the problem of terminal differentiation or the pathology of aging, the extensive work done on the mechanisms intervening in the switch to the terminal postmitotic fibroblast is not discussed herein.

THE UNITY AND INTERDEPENDENCE OF PHENOMENA IN THE ORGANISM

Additional problems have plagued the field of gerontology. The insatiable quest for a Holy Grail, rooted in our culture, has led to attempts to explain aging with regard to a keystone — an initial trigger, followed by a chain reaction leading to senescence. There have been several fads, some at the molecular level such as DNA mutations, cross-links, protein errors, free radicals, etc., and others of a more general nature, such as the influence of stress. This does not fit the physiology of complex organisms regulated by infinite interactions between the different hierarchical orders of organization that constitute them. Hence, it is not surprising that the hypotheses proposed to explain aging, whether of a general nature or focalized at the molecular level, are actually all connected; it illustrates the unity and interdependence of all phenomena in an organism.

Stress as a cause of aging has been proposed by Selye, who postulated that individuals are born with a fixed quantity of adaptive energy which is progressively consumed during the increased exposure to hormones secreted during stress.[36] Selye was able to induce a progeria-like syndrome in rats using dihydrotachysterol, and to prevent it using spironolactone which he termed a catatoxic hormone, i.e., capable of canceling the toxic effects of other hormones.

The stress of reproduction is a major hormone-releasing event in some species — one that triggers a chain of reactions leading to rapid senescence and death. In humans, it was found that castration prolonged the life of inmates in a mental hospital;[37] this could be an example of a mechanism that obviously plays an important role in limiting the life span in some species but became relatively unimportant in others.

It is unquestionable that stress can accelerate aging, not only through the triggering of diseases, but also by hastening changes at the molecular and cellular levels that lead to senescence. An interesting study showed that arterial smooth muscle cells from hypothalamus-stimulated animals grow faster when explanted *in vitro* than do those of the control donors.[38] This work demonstrates the repercussions of a broad reaction in the organism at the molecular, cellular, and tissue levels. It is also representative of the influence external events can have on the proliferative history of a cell compartment.

In addition to or because of its accelerating effect on senescence, stress plays a role in mortality which becomes increasingly significant with aging, since the amplitude of the insult needed to kill diminishes as the organism ages.[39]

The stress hypothesis is a variant, although more specific, of the "rate of living" theory. This theory claimed that the duration of life varies in inverse proportion to the rate of energy expended, as a result of a finite, total amount of "vitality" being used. This proposal eventually acquired a scientific basis when a correlation was ascertained between life span and metabolic rate and temperature.[2]

The way energy expenditure is regulated is a crucial problem in cell biology and one which unfortunately is almost completely unknown to us. The problem of the control of energy transduction and its role in aging is related, at the molecular level, to the proposal that the fundamental cause of aging resides in the mitochondria, the power house of the cell. It postulates that dysfunction of the mitochondria would be due to alterations of the mitochondrial genome, leading to disorganization of free radical production on the mitochondrial membrane.

Free radicals are molecules with an impaired electron. They are generated along the electron transport chain, when electromagnetic energy is transformed into chemical energy. The ultimate electron acceptor along the chain is oxygen, which then becomes a superoxide radical. The goal of

this electron transport is to create chemical energy with the production of a high-phosphate donor, i.e., ATP. This transformation of energy is obviously a crucial process in the life of a cell, therefore anything that takes place in the cell must be influenced by, or influences, this transport chain.

Thanks to oxidative metabolism, molecules are modified — in this way constituting signals for homeostatic molecular and cellular elimination and renewal (see Chapter 6).

The free radical theory of aging has been one of the most popular. It demonstrates how arguments proposed to explain both maximal life span and organism aging can be used indiscriminately to find a single explanation for everything. This has been one of the problems for those interested in learning the methods used to identify the mechanisms of aging: the combination of conceptual contributions made to explain maximum life span with the theories and experiments attempting to explain aging of an organism. Although the two phenomena may overlap in some respects, some mechanisms are proper to each. The correlation between oxidative damage and species life span[40] could provide a mechanism to explain the former rather than the latter.

The role of free radicals in aging-related pathologies is well documented; their influence on the mechanisms of aging, though, has a less firm basis and is difficult to fit into many of the features involved in longevity. The prolongation of the life span, measured as a function of the survival curve of a population of individuals, is usually used to ascertain the causal relationship between aging and a given parameter. However, prolonged survival can be due to the elimination of pathologies that curtail the life span without having an effect on the process of senescence. This has been shown to be the case in the improved survival of calorie-restricted animals.[41] The same could hold true for life span manipulations through the action of free radical metabolism. There are other pitfalls in using survival curves to identify phenomena influencing aging, but they will not be discussed in this volume.

The free radical theory of aging does not explain many features, inter alia the clock-type behavior of the mammalian life span and the parental genetic influence on aging.

Inherited longevity cannot be due to genes either, since accelerated physiologic aging has never been reported. Individuals die before reaching their maximal life span potential because of accidents or disease. Furthermore, all the known so-called syndromes of premature aging actually involve a variety of pathologies and only have a vague similitude with physiologic aging. The Werner's syndrome of so-called premature aging has a very complex genetic picture that has no analogy to physiological aging. All progeroid syndromes seem to be more a deviation from normal development associated with several pathologies than accelerated aging.

The parental influence on longevity could be due to the genetically determined probability of developing or not developing diseases that curtail the life span, rather than to modifications of the process of aging per se. In that case genes would naturally be involved, since a correlation between the presence of certain genes and the probability of developing specific diseases is well documented.

The inherited genetic determinants of longevity could also influence aging through the hereditable character of time, as proposed by Gedda and Brenci.[42] These two investigators suggested that there are two properties for every gene, one consisting of the informational potential which they called the ergon, and the other corresponding to its informational activity period which they called the chronon. They reported an interesting correlation in monozygotic twins as to when different developmental and senescent processes were manifested such as first word, first pubic hair, onset of menarch, first gray hair, use of eyeglasses, or onset of menopause.

Aging is determined from the embryonic stage onward, and the events that occur during development can be critical for the pattern of aging.[43] Longevity could be influenced by the periodicity of the different developmental stages; genetic determinants of this periodicity could, in part, be parentally transmitted. This way, the hereditary determinants of longevity could be related to the phenomenon of hereditary biological time, the chronon.[42]

The constant desire to find a rationale in evolution led to the proposal that specific genes and specific genomic modifications are responsible for species life span, aging of the organism, as well as cell aging. This does not make sense in the face of the complexity of the genome and of its interactions with other levels of information storage.

Genes must be involved in the determination of a species life span, but theories that propose sets of genes as the main determinants of life span seem simple-minded. It is more likely that the whole genome is involved in the determination of a species life span, with the coding and noncoding regions as well as the folding of DNA. The examples mentioned earlier concerning differences between the genomes of humans and rodents support this view. It is becoming increasingly obvious that regions occupied by repetitive sequences are equally important. They have been found to play a role in recombinational events; this may be due to a preferential nicking of DNA in regions of moderate repeats.[10] On the other hand, an increase in the number of certain repeats can destabilize genomic regions and lead to disease.

The genome though, cannot be the sole determinant of the life span in such complex systems as mammalian organisms. As pointed out by Sacher,[44] "the length of life is the expression of the total capability of a set