Gerontogenes: real or virtual?

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ABSTRACT **The view that the life span of an organism is intrinsically limited and is largely species-specific necessarily involves certain notions of genetic elements of regulation. The term gerontogenes refers to any such genetic elements that are involved in the regulation of aging and life span. The existence of genes for programmed aging is generally discounted on the basis of evolutionary arguments against the notion of the adaptive nature of aging. It is suggested here that the concept of gerontogenes be linked with the idea of genes involved in homeostasis and longevity assurance, which is not contradictory to the nonadaptive nature of aging. Because these genes were not originally selected as real genes for aging, their involvement in aging is an emergent property making them virtual gerontogenes. Some experimental evidence is available that suggests that sets of genes involved in the maintenance and repair of various cellular functions are the primary candidates qualifying as virtual gerontogenes.—Rattan, S. I. S. Gerontogenes: real or virtual? *FASEB J.* 9, 284–286 (1995)**

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SOONER OR LATER, ALL INDIVIDUALS DIE. There may or may not be a genetic program that determines the exact time of death, but there appears to be an evolutionary constraint in terms of maximum achievable life span within a species. The view that the life span of an organism is intrinsically limited and lies largely within a species-specific range necessarily implies certain notions of genetic elements of regulation. In this context, the term gerontogenes (1) refers to any such genetic elements that are involved in aging.

The idea of gerontogenes does not contradict the nonadaptive nature of aging. Rather, it reasserts the importance of the genetic mechanisms of somatic maintenance in assuring germ line continuity, as envisaged both by the antagonistic pleiotropy theory and the disposable-soma theory of the evolution of aging and life span (2, 3). Because the existence of gerontogenes as genes for programmed self-destruction is generally discounted on the basis of evolutionary arguments against the notion of the adaptive nature of aging (4, 5), the concept of gerontogenes is intimately linked with the idea of genes involved in homeostasis and longevity assurance instead of certain special genes for aging.

THE NATURE OF GERONTOGENES

The term gerontogenes does not refer to a tangible physical reality of real genes for aging but to an emergent functional property of a number of genes that may influence aging. For this purpose, the term virtual gerontogenes has been suggested (6, 7) in which virtual is defined, as in the Shorter Oxford Dictionary, as something that "is so in essence or effect although not formally or actually; admitting of being called by the name so far as the effect or result is concerned." In science, the term virtual is used for entities that it is useful to regard as being present although they have no physical existence. The paradigm of such an entity is the virtual image of optics. Another example is the currently fashionable "virtual reality," which fulfills the same definition.

The concept of virtual genes therefore refers to the emergent property of several genes whose functions are tightly coupled and whose combined action and interaction resemble the effect of one gene. Treating such a group as a virtual gene is a useful conceptual tool while the search continues for the genetic elements of regulation of complex biological processes such as aging. Although differentiation and development are good examples of highly complicated and complex systems involving many genes, the concept of virtual genes may not apply to them because these processes are under direct genetic control and have evolved as a result of natural selection. This situation is unlike aging where no natural selection for any specific genes is envisaged. Therefore, the concept of virtual genes is appropriate only for phenomena such as aging where a genetic involvement is expected without direct genetic control open to natural selection.

The idea of gerontogenes as virtual implies that each time a gene is discovered that appears to have a role in the process of aging, it will, on sequencing and identification, turn out to be a familiar, normal gene with a defined function. Its role as a gerontogene can be realized only in the context of its emergent property in relation to several other genes that influence its activity and interactivity. Such genes cannot be hidden because their identities can, in principle, become well known. Individually, the functions of such genes can be clearly established. Yet as a result of concerted action and interaction, the combined effect of these genes resembles that of a "gene for aging" although they were not especially designed or naturally selected to cause aging. This idea of virtual gerontogenes is in keeping with the evolutionary explanation of the process of aging as an emergent phenomenon owing to the lack of eternal maintenance and repair rather than to an active and adaptive process.

EVIDENCE FOR CANDIDATE GERONTOGENES

Obviously not every gene is potentially a virtual gerontogene. However, every gene can potentially affect the survival of an organism. Therefore, a distinction must be made between immediate survival or death and the process of aging. Knocking out any essential gene will result in the death of an organism without having anything to do with the process of aging.

For virtual gerontogenes, one could narrow the possibilities to sets of genes involved in the maintenance and repair of the cellular and subcellular components as the primary

[1]Abbreviation: SOD, superoxide dismutase.

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candidates for qualification as virtual gerontogenes. This is because almost all theories of aging imply directly or indirectly that the progressive failure of homeostatic mechanisms is crucial for the process of aging. For example, theories emphasizing the accumulation of somatic mutations, the buildup of oxidative damage in macromolecules, the accumulation of abnormal, erroneous, and defective proteins, deficiency of the signal transduction pathways, deficiency of the immune system, and several other similar hypotheses all point to the failure of maintenance at all levels of organization as a crucial determinant of aging and life span (8–10).

Evidence for the hypothesis that candidate virtual gerontogenes operate through one or more mechanism of somatic maintenance and repair comes from experiments performed to slow down aging and increase the life span of organisms. For example, antiaging and life-prolonging effects of calorie restriction are seen to stimulate various maintenance mechanisms. These include increased efficiency in DNA repair (11), increased fidelity of genetic information transfer (12, 13), more efficient protein synthesis (14–16), more efficient protein degradation (17), more effective cell replacement and regeneration, improved cellular responsiveness (18), fortification of the immune system, and enhanced protection from free radical- and oxidation-induced damage (19–21). Genetic selection of *Drosophila* for longer life span also appears to work mainly through an increase in the efficiency of maintenance mechanisms, such as antioxidation potential (2, 22–24). An increase in life span of transgenic *Drosophila* containing extra copies of Cu-Zn superoxide dismutase (SOD) and catalase genes is primarily due to enhanced defenses against oxidative damage (25). Similarly, antiaging effects of carnosine (26), a dipeptide, and kinetin (27), a cytokinin, on human diploid fibroblasts also appear to be due to the effect of these chemicals on maintaining the efficiency of defense mechanisms, including efficient protein synthesis and turnover and the removal of oxidative damage.

Attempts to identify determinants of longevity by finding a correlation between maximum life span of a species and certain biological characteristics have also shown that it is the efficiency of various defense mechanisms that correlates best with longevity (28). Some of the well-known maintenance mechanisms whose level of activity and efficiency are directly correlated with species life span include DNA repair (29–31), cell proliferative capacity (32, 33), and antioxidative potential (34–37).

Further experimental evidence in favor of the concept of virtual gerontogenes comes from several studies to identify senescence-specific genes in old cells and tissues. Almost all such studies have resulted in the identification of genes, such as those of the components of the extracellular matrix, that are known to have other functions in cell metabolism and physiology (38–41). Studies of the extension of life span and slowing down of various age-related biochemical and functional alterations of *Drosophila melanogaster* by simultaneous overexpression of Cu-Zn-SOD and catalase (25) indicate that these free radical-scavenging and antioxidant genes are part of the gerontogene family by virtue of their role in influencing aging and life span.

The identification of the long-lived mutants of the nematode *Caenorhabditis elegans,* involving the *age-1* (38, 42–44), dauer-constitutive *daf-2* (45), and spermatogenesis-defective *spe-26* (46) genes may provide other examples of virtual gerontogenes. Although the exact nature of the final protein products of these genes is now unknown, characterization of the *age-1* mutant strain of *C. elegans* has shown increased resistance to hydrogen peroxide-induced oxidative damage and an increase in the activities of SOD and catalase enzymes in the mutants (47). Other possibilities may be found in the complex regulatory mechanisms known to exist in connection with the end-replication problem of telomeres (48) and the postreplicative processing of DNA, such as methylation (49). Molecular studies using a comparative approach, including the use of transgenic organisms, will be useful in identifying most genes important in this respect and can form the basis of developing appropriate strategies for future gerontological research.

IMPLICATIONS FOR AGING RESEARCH

The objective of this article is to develop the concept of virtual genes in aging as an emergent property of several functionally coupled genes that were not naturally selected to cause aging, but whose combined action and interaction reveal their role as gerontogenes. Therefore, to unravel the genetic elements regulating the aging process, studies should be directed toward understanding the mechanisms of interaction and interdependence of various genes involved in maintenance and repair.

The phenomenology of aging is rich in empirical data showing that individually no tissue, organ, or system becomes functionally exhausted even in very old organisms, yet their combined interaction and interdependence determines the survival of the whole. The same logic needs to be applied for studies of the molecular and genetic levels. Searching for an all-encompassing aging gene (or genes) is unlikely to be successful. Estimates of the number of genes that could influence aging and life span run to a few hundred of about one hundred thousand genes, and their allelic variants, in mammalian systems (50). A search for universal biomarkers of aging is likely to be unsuccessful because of the astronomical number of ways in which such interactive units or networks can manifest stochastic alterations.

Therefore, manipulating any single gene or a few genes that show some effects on aging and life span will help to identify genes that might qualify as being a part of the virtual gerontogene family. Of course, such studies will be valuable to find ways to fine-tune the network and to prevent the onset of various age-related diseases and impairments by maintaining the efficiency of homeostatic processes. In the short term, such studies will also result in developing a variety of so-called antiaging products by concentrating on the individual members of the gerontogene family. In contrast, direct gene therapy of the total aging process seems to hold little promise. To unravel the molecular basis of aging and modulate the process, the most promising research strategies will incorporate an analysis of the formation and functioning of maintenance and repair networks. The concept of virtual gerontogenes can be useful to design new experiments and help to search for the genetic "hand of cards" that provides the best possible combination to prevent succumbing to perturbations from internal and external sources. FJ

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