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Quest for a Long Life: Paradoxes and Essentials of Evolving Longevity

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Among the countries in the developed world, Japan has the longest mean lifespan for women; however, the nation has encountered serious problems in policy and economics, as well as in managing medical care for its aging population. Aging is inevitable, but it also constitutes a major challenge in modern biology and medicine. In the treatment of geriatric patients, an understanding of the fundamental biological mechanisms of aging and longevity is crucial for the effective treatment and prevention of diseases and disorders, including dementia, osteoporosis, and sarcopenia. To address the most basic questions about aging, including determinants of lifespan and the identity of critical genes and anti-aging factors, we discuss paradoxical phenomena in the biology of longevity, with a particular focus on "time" and "size" of organisms. We also discuss essential factors and/or activities associated with anti-aging mechanisms in connection with brain function in adults and the elderly. Finally, we discuss unique features of the *Shc* gene family, which is involved in longevity determination, brain size restriction, cognitive functions, and evolution. The aim of this paper is to offer some insight into various problems in gerontology and geriatrics for future research. (190 words)

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As one grows older, one becomes wiser and more foolish.
Francois duc de La Rochefoucauld (1613-1680)

Introduction

We all live at a given point in time and history, but we also construct our own history in our life (see Fig. 1). In humans, life history is long and complex, and quality of life (QOL) is a serious concern for those who live a long life.

Aging is the life stage that immediately follows maturation. Almost all multicellular organisms, particularly in the animal kingdom, are the product of sexual reproduction, beginning with the fertilization of an egg by a sperm and followed by differentiation and development, which include many processes that are primarily determined genetically. Species-specific traits and developmental processes are coded in the deoxyribonucleic acid (DNA), or the genetic material, of each species. In contrast, the question of whether aging is programmed similar to development or whether it is solely a stochastic process is controversial [1,2]. Recent molecular genetic studies, however, have clearly demonstrated that there is a set of genes that play a role in controlling animal longevity [3,4].

Lifespan is thus determined, at least in part, by longevity genes, but these genes may also affect the aging process. During our long lifespan, humans are susceptible to various life-stage-specific diseases. Some diseases affect development and maturation, resulting in shortened lifespan, and some affect aging and/or senescence, causing deteriorative changes in organs and tissues. Both types of diseases are relevant to gerontology and geriatric medicine (Fig. 1) Although there are many diseases associated with aging,

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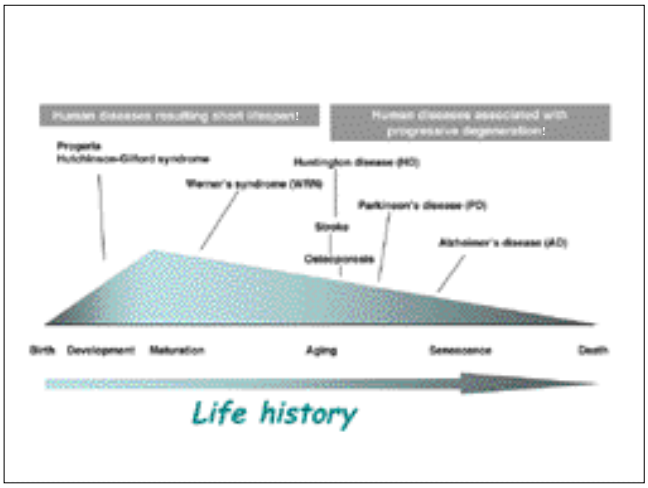

Figure 1. Life history and diseases related to aging.
In all animals, including humans, the life history stages that occur between birth and death are development, maturation, aging, and senescence. The total duration of these stages constitutes the lifespan of the animal. Representative examples of aging-related diseases are shown along the schematic drawing of human life history. The diseases can be classified in two categories: the first set includes Hutchinson-Gilford syndrome (progeria) and Werner's syndrome, both of which result in a shorter lifespan. The second set includes osteoporosis, stroke, and Huntington's, Parkinson's, and Alzheimer's diseases, which are progressive disorders that occur in later stages in life. Aging itself is a critical risk factor for those diseases; thus, they are known as age-related degenerative diseases.

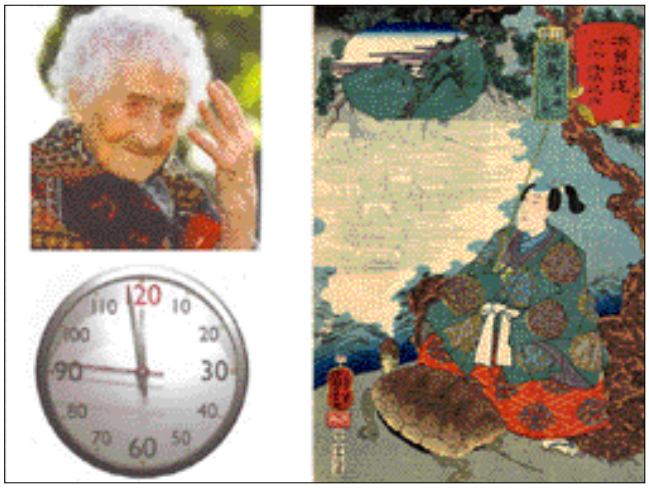

Figure 2. Urashima, Calment and the clock of aging.
Taro remembers *Ryugujo* castle (right). The *Urashima* story was written in the 17th century, in the Eydo period, and collected in a book entitled *Otogi-zoshi*. Ms. Jeanne Calment, French-Canadian super-centenarian, celebrating her 122nd birthday (the original image was listed in the Jeanne Calment image results from Yahoo) (left-top). An image of a clock of aging that spans 120 years (left-bottom).

there also appears to be a natural, genetically programmed maximum lifespan for humans. The person with the longest recorded lifespan was a French woman named Jeanne Calment, who lived for 122 years and 164 days and showed no signs of geriatric diseases [5] (see Fig. 2).

Humans thus have the potential to live approximately 120 years, but it is unknown whether this "time" resides in our own body, or how is it being sensed in our life and/or in our body.

The Urashima story: A hidden clock for aging?

In a Japanese fairy tale entitled *Urashima-Taro* (Fig. 2), *Taro*, a young fisherman, was riding on the back of an enormous turtle when the animal dove deep into the ocean in pursuit of colorful fish. The turtle carried *Taro* to an underwater castle called *Ryugujo*, where the fisherman was welcomed as a delegate from beyond the ocean. *Taro* enjoyed glorious foods, fantastic dances, plays, and the companionship of beautiful women, but although his stay seemed to last only a few days, years passed in the world outside. When *Taro* decided to return home, the sea people gave him a gift box and told him never to open it. *Taro* returned to his home village and to fishing, but one day, remembering *Ryugujo* and the box, he decided to see what was inside. When he opened the box, white smoke billowed out, and *Taro* was transformed into a white-haired old man [6]. We do not know how old *Taro* was after he opened the box, but he might have envied Jeanne her long life (see Fig. 2).

Generally speaking, the clock of aging, if it is to be found in the body, should proceed at a constant speed. In *Ryugujo*, the clock of aging had stopped or slowed down; when a catch of the clock was released, time progressed rapidly for *Taro*. In the real world, the clock of aging may also move at different speeds under different conditions. In other words, the clock can be regulated.

We do not yet know where the clock is located within the body; however, the question of how it can be regulated is gradually being answered.

The paradox of the clock: circadian vs. aging

We know about the existence of the circadian clock [7,8]. This intrinsic clock is found in the brain and roughly senses biological rhythms that are entrained to the light-dark cycles of the environment 24 hours a day. The associated region is the suprachiasmatic nucleus (SCN), a miniscule area hidden at the base of the cerebrum. The French philosopher

René Descartes mistakenly predicted that the circadian clock would be found in the pineal gland, which he thought was located near the surface of the brain (and thus near light) [9,10]. The discovery of the circadian pacemaker in the SCN, which is deep in the brain, would therefore have come as a surprise to Descartes. A set of genes that encode proteins that pace the circadian rhythm of the clock are also now known [11,12]. The circadian clock genes, however, are not connected to aging. The "day clock" and the "life clock", both of which govern the biological rhythms of organisms (including humans), operate at completely different levels.

Where, then, is this "life clock" that paces growth, development, and aging? It may be located in the brain, likely near the hypothalamus, although current research has yet to find direct evidence of this arrangement. Humans certainly sense the passage of time; we can instantly distinguish delay from promptness, yesterday from tomorrow, and the remote past from the near future.

The current scientific consensus, however, does not include time among the five senses, possibly because we do not have receptors for time. It may be that such receptors exist, but we merely lack the knowledge of them. If this is the case, we may discover these receptors in the near future, just as we discovered the pacemaker in the SCN, which was unknown to Descartes. Although we know more about the circadian clock than Descartes, we have yet to find the hypothesized "life clock".

The paradox of body size and longevity: inter-species vs. intra-species

Organisms' lifespans vary greatly in length [13,14]. Even among human beings, some live to very old age, and some die young. In developed countries in Europe, North America, and East Asia, the mean lifespan is approximately 75 to 85 years and is increasing. The maximum lifespan of humans is estimated to be approximately 120 to 125 years [15].

Interestingly, in the animal kingdom, or at least in vertebrates, there is some correlation between the size of the animals and their lifespan; small animals die young, and large animals live longer [13,16] (Fig. 3A). The average lifespan of mice is 3 to 4 years, but cats and dogs live ten to fifteen years, and non-human primates (including chimpanzees) live 30 to 60 years.

This trend should not necessarily be surprising if we consider the processes of development and maturation in these mammals. Animals take time to reach maturity. The development of mammals, for example, starts with fertilization, with subsequent cleavages and embryonic development before birth. The infant then grows through childhood and adulthood. Throughout these processes, the body grows larger; cell division takes time, and development does as well. Thus, the time to maturation and death is naturally longer in larger animals, and larger animals have longer lifespans.

For social animals, such as humans, physiological maturity is not necessarily the last stage of growth because mental capacity continues to mature. Social, personal, and mental growth continue even after the completion of physical maturity. This process is in part the result of genetically determined programs that ensure that parents support and nurture their children. In females, the period from birth to menopause is almost twice as long as the period from birth to physical maturity. In terms of procreation, menopause signals the end of the "expected" lifespan; however, social animals continue to grow socially, influencing the next generation. This notion, which is, in part, related to the so-called "grandmother effect" [62], is of interest for considering the genetic influence of post-menopausal periods to the evolution of human aging. Thus, mammals, including humans, take a long time to fully mature in both the physical and the social sense. Their lifespan, therefore, must be long enough to allow for both physical and mental growth. For this reason, social animals have longer lifespans.

Generally speaking, thinner individuals live longer than fat individuals. This trend is the inverse of the previous size-related rule; the smaller species have shorter lifespans than the larger species, but within species, the smaller individuals tend to live longer than the larger individuals (see Fig. 3B). Overweight is not generally a healthy condition,

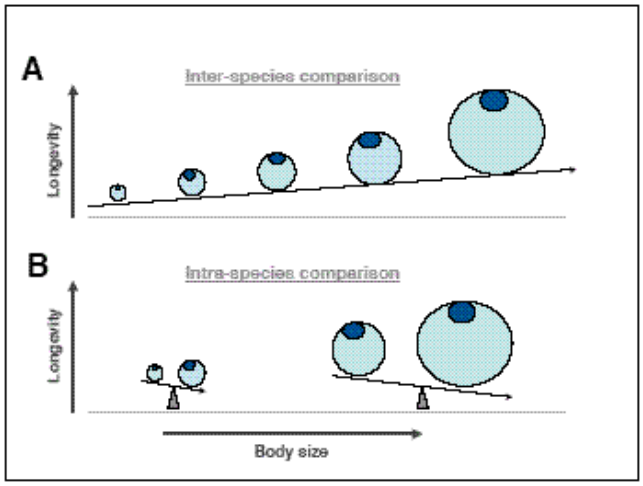

Figure 3. Correlations between body size and lifespan in animal species.
(A) Inter-species comparison; (B) Intra-species comparison. Note that the correlations are inverted in A and B.

and limited caloric intake is beneficial to the quality of life and longevity.

As discussed above, there is a correlation between body size and longevity; however, the outcome differs depending on whether the comparisons are made among species or within species. A likely hypothesis is that, during evolution, body size becomes larger and larger as one species evolves into a new species. Within a species, however, a relatively smaller body size may be favored as an environmental adaptation. There may be some genes that favor the development of smaller body sizes, allowing organisms to adapt to environmental stress.

Co-evolution of the lifespan and the brain

As previously mentioned, larger animals tend to live longer. An even stronger correlation is seen in the relationship between the lifespan and brain size of the organism. Animals with larger brains generally live longer [17,18].

The primate brain evolved rapidly [18-20]. After humans and chimpanzees diverged from a common ancestor approximately 8 million years ago, the evolving human brain tripled in size, with marked encephalization in the frontal and temporal lobes compared with the brains of chimpanzees. During this period, the human lifespan also increased nearly three-fold. Does this set of changes suggest that the brain determines, or at least affects, lifespan? Scientifically, it is difficult to draw any conclusions from the apparent correlation.

The brain performs several functions, and one important function is the control of the body. The entire body, except for the brain itself, is under the control of the brain, which is the operational center of the central nervous system. In the brain tissue, the hypothalamus and brain stem are the most crucial regions for body control. The hypothalamus is believed to be responsible for controlling appetite, body temperature, and sexual desire. Similarly, neural networks in the basal ganglia precisely gauge and regulate the skeletal muscles, controlling posture and behavior. Thus, the hypothalamus is the guardian of the visceral system, and the basal ganglia play a similar role for the skeletal system. The reticular formation in the brain stem regulates functions essential for life, such as the heartbeat and respiration. Thus, these lower brain regions act as the control center of the body.

Another important function of the brain is to sense the external world. We see our surroundings with our eyes via our retinas; however, perception, or the conscious recognition of sight, occurs in the brain. This is the case for all of the five senses. The brain absorbs information from the outside world through five sensory receptor types and uses that information to access the surrounding environment and to determine how to act in a given situation.

Next, the brain makes decisions regarding the organism's behavior. This function requires learning and memory, which are higher brain functions that are centered in the limbic system and the cerebral frontal cortex. It is thought that memories emerge from the hippocampus and are stored in the neural networks of the cerebral cortex [21,22]. The highest function of the brain is consciousness [23,24]. The precise mechanisms of consciousness and memory storage are currently unknown, and further investigation is required. Nonetheless, we assume that higher cognitive abilities and/-or intelligence should help some organisms survive in their environments [25,26]. Animals with larger brains live longer. Thus, the evolutionary acquisition of larger brains must have resulted in a longer lifespan. We assume that primate evolution prioritized the acquisition of superior brain-power, *i.e.*, intellectual evolution, over muscular power, *i.e.*, physical evolution. Intelligence would have improved survival through natural selection; thus, the size and/or quality of the brain would correlate with lifespan.

Anti-aging strategy based on the brain mechanisms

If the brain regulates lifespan, does it also control the aging process? Before we discuss this issue, we first need to clarify the difference and the relationship between aging and lifespan. Many people consider aging and lifespan to be equivalent concepts, but aging is a process, whereas lifespan is a period of time that ends with death. If aging proceeds more slowly, lifespan increases, and as lifespan increases, aging slows. Thus, aging and lifespan are inversely correlated.

If the brain determines lifespan, we can assume that it also determines aging. Many genes that control lifespan also affect processes that are related to aging. These gene products control lifespan by controlling factors involved in the aging process. As previously mentioned, brain size correlates strongly with longevity; therefore, the brain should be targeted in anti-aging research.

Currently, a variety of so-called "anti-aging" products, such as skin care products and supplements, are available on the market. A more effective and scientific approach, however, would be to target the brain's "anti-aging" functions (Fig. 4). As the brain is the control center of the body,

longevity-associated genes expressed in the brain are critically important for "anti-aging" functions. A mere skin cream cannot protect against aging. Medical intervention to protect the aging brain may be the key to improving QOL in the elderly [26].

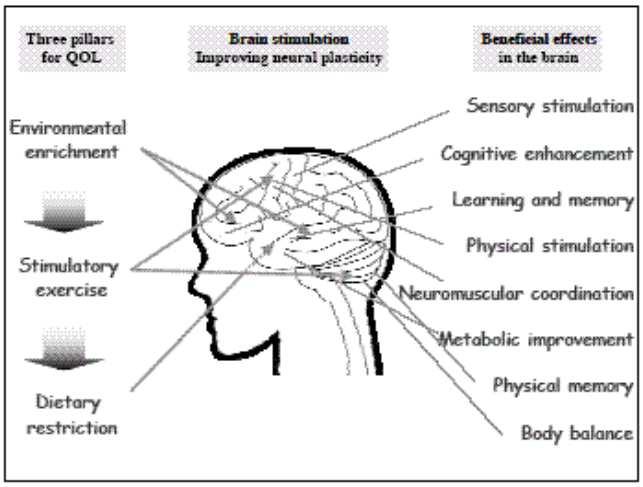

Figure 4. Brain stimulation is key for preventing aging. Hypothetical pathways and networks in the brain are shown that could improve quality of life via neural circuit stimulation by the three essential anti-aging factors.

Essences for senescence or anti-aging

Over the last several decades, gerontologists have conducted studies using various approaches to find efficient anti-aging strategies, seeking to promote prolonged lifespans with higher QOL. Three important factors in aging became evident from those studies: diet, environment and exercise (Fig. 5).

Diet: Lower caloric intake is protective against aging, provided that nutritional requirements are satisfied [27,28]. Most laboratory animals, *e.g.*, rats, mice, flies, nematodes, or yeasts, are fed *ad libitum*. Laboratory mice enjoy buffet-style meals every day, a lifestyle that is quite different from our own. It is now generally accepted that so-called "caloric restriction" (CR) and/or "dietary restriction" (DR), with a calorie intake limited to 70% of the baseline, extends the lifespan of these mice by 10 to 30 % [27,28]. Humans may occasionally enjoy buffet-style eating; however, we usually limit the meal to, for example, breakfast or lunch, and we do not eat more than we need, except on special occasions.

The effects of CR or DR have mostly been explored in laboratory mice. There have also been several studies on the effects of caloric restriction in primates [29,30]. In humans, a group of people in the United States attempted CR themselves, hoping for a longer lifespan [31,32].

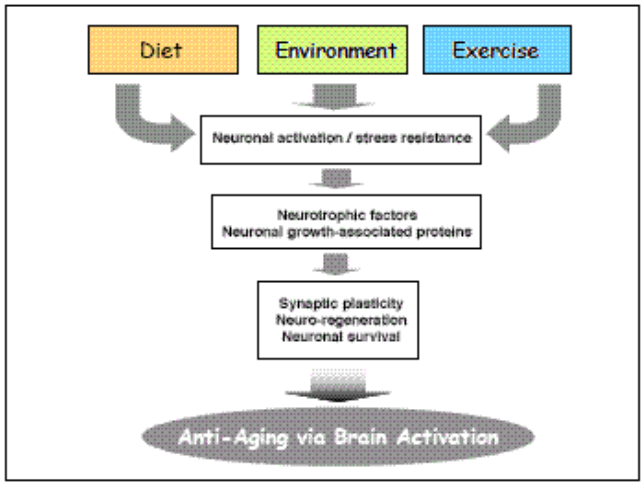

Figure 5. Essential factors for the prevention of aging. Reduced caloric intake, enriched environment, and stimulatory exercise are considered the three pillars of an effective anti-aging strategy. All of these factors modulate brain function, gene expression, and neural plasticity, which ultimately lead to the activation of anti-aging pathways, via beneficial changes in brain function.

Environment: In addition to diet, environment was found to be a key factor in determining longevity. If laboratory mice were taken from a conventional stainless steel cage and placed in another cage filled with a variety of toys, *e.g.*, wheels, bridging boards, swings, and hanging ropes (see Fig. 6A, B), their brains become more active and better able to retain memories and learning. The so-called "enriched environments" contribute to improved cognition and

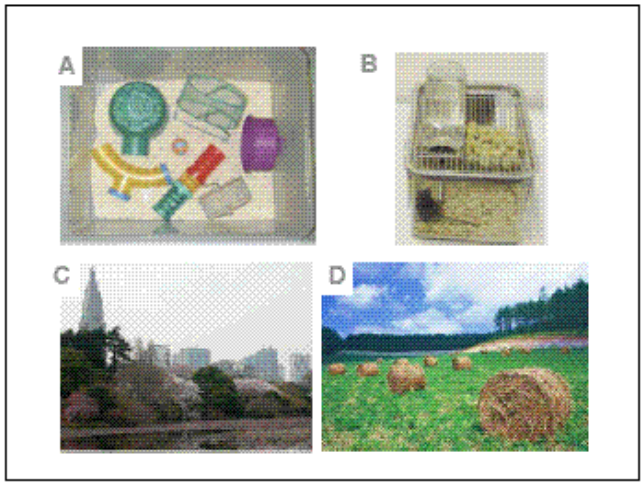

Figure 6. Mice and humans: which environment is better enriched? (A) A mouse cage with an enriched environment; (B) the standard cage for laboratory mouse. Note that drinking water and food (pellets) are provided *ad libitum*. (C) Urban city (Tokyo, Japan); (D) Countryside (Hokkaido, Japan).

even to the synthesis of new neurons from stem cells [33-35]. These newly generated neurons are integrated into new neural networks by functional synapses [36,37].We are not sure, however, how this study applies to humans who live in highly enriched city environments compared to those who live in the country (Fig. 6C, D). City life can be stressful, and country living can sometimes be peaceful but also tedious or monotonous. It may be difficult to adjust one's lifestyle to the desired levels of "enrichment", balancing stimulation and stress.

Exercise: There is yet another factor associated with longer lifespans with higher QOL: stimulatory exercise at modest or moderate levels. The enriched environment may automatically initiate this "stimulatory exercise" effect. Overwork, however, must be avoided because fatigue does not promote long life. Thus, exercise should be employed in moderation, as should nutrition and stimulus. Overstimulation results in stress, which has harmful effects. Thus, QOL depends on moderate levels of all three factors.

Neural stem cells and progenitors: Recovery for the aging brain?

What neural cells or components are most affected by dietary restriction, environmental enrichment, and stimulative exercise? Stem cells and progenitors are reasonable candidates. Neural stem cells and progenitors are abundantly present in the embryonic and/or developing brain; however, they also persist in the adult brain, albeit at an extremely low level [36-39], and are even still present in the aging brain [63,64].

Neural stem cells are activated by the aforementioned three stimuli, *i.e.*, dietary restriction, environmental enrichment, and exercise in adult animals [33-35,40-46]. Under these stimuli, the number of neural progenitors and new neurons generated from stem cell populations increases several fold in certain brain regions; these cells are likely integrated into the pre-existing neural networks, thus forming new neural circuits in the adult brain. The best-studied cell populations are the stem cells in the dentate gyrus of the adult hippocampus. It is, however, still under investigation whether and how those neural stem cells and neuronal progenitors are activated, how they migrate, and how they are further integrated into the existing neuronal circuits in the hippocampus [36,40]. It seems certain that some populations of those progenitor-derived new neurons enhance synaptic plasticity in the adult brain [41]. Synaptic plasticity, in the form of long-term potentiation (LTP) in the hippocampus, is fundamental for learning and memory. Mounting evidence indicates that newly generated neurons are required for memory acquisition and elimination (36-41,47). Fred Gage and his colleagues propose the following interesting hypothesis: adult neurogenesis in the dentate gyrus in the hippocampus may contribute to encoding time of new memories [48]. As we argued previously, "time" is the most fundamental and essential factor in considering aging. How do we measure time? How do we sense time? The way in which "time" is incorporated into the long-term episodic memories in our daily life is a central problem in understanding memory formation. The neural stem cells in the dentate gyrus of the hippocampus are a very minor population in the adult brain; however, the maintenance of this small fraction of cells over the course of a long life is a critical issue for the aging brain.

An understanding of the mechanisms that maintain the stem cells in adult and aging brains would thus be crucial to a better understanding of the potential reservoir of cells; this resource could be used to fight neural degeneration, a major deteriorative process in the aged brain, and/or reconstruct damaged areas (see Fig. 1). While many genes cooperate to form and regulate stem cells, Shc signaling (see below) contributes significantly to the coordination of the differentiation of neural progenitor cells [49].

Shc: A gene controlling lifespan and brain size in mammals

Previously, we discussed the relationships among the body size, brain size, and lifespan in animal species. The lifespan correlates with body size and, more significantly, with brain size. However, recent investigations have revealed essential genes whose expression and/or functions are highly correlated with lifespan [3,4,50]. Is there then a gene whose function correlates with lifespan and with brain size as well?

Interestingly, *Shc* might be associated with such a connection and is a candidate gene that might have affected or played a role in the evolution of longevity. The Shc-encoded proteins p66-Shc and p52/p46-Shc are important in signaling events during differentiation, maturation, diseases, and aging (for reviews, see [51-54]). The most notable evidence of their importance in aging is that a gene knockout mutation in p66-Shc may modulate lifespan in mice; a mouse line deficient for p66-Shc had a longer lifespan compared with the wildtype control [55]. Another important piece of evidence is provided by a transgenic mouse line that

expresses mutant p52/p46-Shc with a tyrosine/phenylalanine (Y/F) replacement in the brain, which presented with microencephaly, i.e., a small brain with thinner cerebral cortical laminas [56]. The Shc Y/F mutant is a dominant negative form of the protein that perturbs the original function of Shc in the brain. Both p66-Shc and p52/p46 Shc are derived from a single *Shc1* gene, which is located on chromosome 3 in mice and chromosome 1 in humans.

Shc is expressed in most tissues but is not known to be expressed in the mature brain. Shc, however, is expressed in neuronal progenitors in the developing brain and possibly also in the adult brain. The Shc Y/F mutant could affect neural differentiation and maturation by perturbing phosphotyrosine-mediated signaling in the developing brain, resulting in microencephaly; in the affected mice, brain weights were reduced to approximately 50% of the brain weights of the littermate controls throughout postnatal and adult life. A similar study on the effects of the Shc Y/F mutant on neuronal progenitors was conducted by Ponti *et al*. in Italy, which focused on the limitations of the proliferative capacity of the neural stem cells in the adult brain [57].

These results reveal a unique role for the Shc gene that could affect both animal lifespan and brain size, which suggests that this type of gene could have been involved in the evolution of longevity.

Epilogue

In the history of evolution, many innovations (variations and mutations) and a few inventions (synthesis and genesis) have occurred. The acquisition of genes or DNA and the gene expression system, particularly transfer RNA (tRNA), are among the inventions. Similarly, we assume that the acquisition of the tyrosine phosphorylation signaling system as a novel modulatory platform for regulating protein functions and dynamics during metazoan evolution may be another indispensable invention [58,59]. Shc is a unique adaptor molecule that is involved in phosphotyrosine signaling and plays crucial roles in cellular differentiation, growth, the stress response, and apoptosis. As described above, Shc might have played an important role during evolution by controlling brain size as well as lifespan. In the brain, however, Shc/ShcA (encoded by the *Shc1* gene) is expressed at lower levels than other Shc members, *e.g.* ShcB, ShcC, and ShcD, which are encoded by the *Shc2*, *Shc3*, and *Shc4* genes, respectively, are known to be expressed in various regions in the adult brain and likely have a variety of roles following the activation of various receptors [60,61]. Further studies on these ShcB, ShcC, and ShcD proteins would shed light on strategies and mechanisms for retaining better QOL in later stages of life. These proteins could be good targets for anti-aging therapies in the brain.

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