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MINI-REVIEW

Aging as a Programmed Process or Result of Wear and Tear (Stochastics): The Dichotomy that Excludes Simple Non-Obligatory Dysregulation as a Root Cause of Aging

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Abstract—In the 1990s, Vladimir P. Skulachev, a proponent of the genetic program of aging, proposed extending the concept of programmed cell death (*apoptosis*) to the level of an entire organism, a phenomenon he termed *phenoptosis*. According to his terminology, *rapid phenoptosis*, is characteristic of species with a single reproductive cycle, such as pink salmon and mayflies, whereas s*low phenoptosis* is typical of species with multiple reproductive cycles, including humans. Interestingly, rapid phenoptosis resembles obligate apoptosis observed during development, such as the disappearance of pharyngeal slits, tail, and interdigital webbing in human embryo. Slow phenoptosis is more akin to non-obligate apoptosis, which is triggered by irreversible damage or functional cell redundancy. Just as non-obligate apoptosis is not inevitable, a similar non-inevitability should not be excluded for slow phenoptosis – that is, natural aging. This interpretation is supported by the plasticity of aging, the reversibility of age-associated traits, and the absence of the replicative (Hayflick) limit in tissue stem cells, a feature they share with immortalized cells. Additionally, human (and animal) mortality patterns resemble those of non-aging hydras and immortalized cells subjected to suboptimal conditions. It has been said that a "correctly posed" question endures indefinitely. In our view, the question "Is aging programmed or stochastic?" falls into the category of "correct" questions. Its apparent dichotomy excludes the obvious third option: in many species with repeated reproductive cycles, aging is associated with neither genetic program nor purely stochastic damage, but rather results from cumulative consequences of living under conditions that are pessimal for stable, non-aging functioning.

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INTRODUCTION

In 2024, participants of the Gordon Research Conference on the Biology of Aging discussed contemporary views on causes and mechanisms of aging, as well as their individual interpretations of the essence of this process. The results were discouraging. As presented in a joint article analyzing the various opinions, the divergence of perspectives on aging proved to be remarkably high [1].

Indeed, while the pioneering works by D. Harman and N. M. Emanuel on the role of free radicals in the 1950s and by Leonard Hayflick and his followers on the primary role of cellular aging in organismal aging in the 1960s had laid the basis for a logical concept on causes and mechanisms of aging, it has later become evident that these steps were not in the entirely right direction.

For example, suppression of free radical processes has been shown to extend lifespan only slightly and only in individs with impaired physiology [2, 3]. In individs with a normal lifespan, such suppression either had no effect [3] or even shortened the lifespan [2], because reactive oxygen species, at appropri-

ate concentrations, act as essential second messengers necessary for harmonious organism functioning.

As for Hayflick's phenomenon of cellular aging, the observed slowdown and eventual cessation in population doublings during serial passaging of cultured cells have not been confirmed at the organismal level. Instead, these effects appear to be artifacts of *in vitro* culturing or are associated with terminal differentiation. In many differentiated cell types (e.g., neurons, corneocytes), cell division is deterministically blocked as part of the normal development. This phenomenon led A. M. Olovnikov, who in the 1970s explained the Hayflick limit by telomere shortening, to abandon his hypothesis that telomere shortening causes organismal aging in 2003 [4] and turn to the development of alternative hypotheses of aging.

Using immunosenescence and cellular zones traditionally considered non-renewable as examples, here we present evidence suggesting that aging can be regulated within broad limits and may be a non-obligatory process.

ON THE DIFFERENCES BETWEEN THE TERMS IMMUNOAGING, IMMUNOSENESCENCE, AND INFLAMMAGING

For a Russian speaker, the terms *immunoaging* and *immunosenescence* appear identical and interchangeable, as both *aging* and *senescence* translate to Russian as "aging" ("старение"). However, their meaning is different: *aging* refers to changes in age, the process of becoming older. In its early stages, age-related changes are primarily associated with development, so aging as age-associated deviation of structural and functional capacities from the norm is generally not associated with this stage. *Senescence*, however, is true aging. Its initial stages are typically manifested after completion of development and attainment of maturity. Only then does a gradual increase in all traits characteristic of this aging process take place.

The thymus, as the central organ of the immune system, begins its involution long before maturity, which is often interpreted as an early manifestation of genetic program of aging. However, thymus involution (*immunoaging*) appears to be related to its role in the organism growth and development rather to aging itself [5]. The true *immunosenescence* emerges only after maturity, leading to inflammatory aging (*inflammaging*) by the age of 50-60 [6, 7].

We should mention that before its recognition as the primary immune organ, the thymus had been known as the "growth gland," or "childhood gland," for several decades. From puberty to full maturity, the regulatory reduction in thymic mass and functional activity serves to slow the rate of somatic growth and occurs at the highest rate across the entire life cycle. This early involution of the thymus (*immunoaging*) is not a part of the organism's aging program, but rather a normal stage of organismal development [5]. Such immunosenescence (*immunoaging*) is physiological and should be distinguished from true dysregulatory immunosenescence (*immunosenescence*), which develops after maturity.

True immunosenescence (*immunosenescence*) is associated with the fact that the thymus is a target organ of the somatotropic hormone produced by the anterior pituitary, the secretion of which declines with age. This unnecessary and dysregulatory decrease occurs because under conditions of human civilization (for humans) or captivity (for laboratory animals), vital functions of the organism are regulated by control systems operating in an unstable mode, with main indicators drifting toward weakening of most functions.

After passing through non-obligatory yet, under these conditions, inevitable stages of immune decline, true immunosenescence progresses to inflammatory aging (*inflammaging*). This phenomenon has attracted considerable attention as one of the negative manifestations of aging [6, 7]. However, inflammaging is not the cause of aging but merely one of its consequences [5, 8-11]. It typically becomes noticeable only during the second half of life and predominantly among residents of economically developed countries as a lifestyle side effect [7]. Consequently, *inflammaging* should not be regarded as an obligatory characteristic of the second half of human life.

There are grounds to believe that immunosenescence, which is observed after maturity (*immunosenescence*), may also be a non-obligatory feature of an organism, similar to what has been proposed for inflammatory aging (*inflammaging*) [5, 8-11].

PHYSIOLOGICAL REGENERATION OF "NON-RENEWABLE" CELLULAR ZONES

It is commonly believed that some organs and tissues contain regions where cellular renewal does not occur. Cells in these zones include, for example, neurons in the brain and cells in ovarian follicles. Therefore, it is assumed that the natural loss of neurons and their age-related changes increase the organism's vulnerability and contribute to aging or even represents its primary cause. Age-related changes in "dormant" oocytes in follicles and the depletion of their pool, which is established in early ontogeny, are considered the main factors underlying age-related decline in fertility and the onset of the postmenopausal period.

However, stem cell precursors have been found for both brain neurons and ovarian follicles [12, 13]. Like all stem cells, they are not subjects of proliferative (Hayflick) limit and can effectively renew cellular compartments previously considered non-renewable. The age-related decline in their cellularity is not related to their "non-renewability," because a similar reduction in cell numbers (cytopenia) is also observed in tissues with continuous turnover, such as the epidermis and bone marrow. Importantly, these changes can be reversed at both tissue [14] and organ [15] levels. There is also evidence of cardiomyopathy reversibility under conditions reducing the load on the heart muscle, such as after sessions of artificial circulation [16, 17].

These results, along with other evidence, suggest that the root cause of systemic age-related cytopenia is not an inherent inability of the organism's cellular compartments to self-maintain and self-repair. Most likely, it arises from dysregulation of processes occurring when the aging body operates outside the zone of stability of its vital functions [8-11].

This explains the age-related decline in the potential for physiological and reparative regeneration; however, there is evidence that this decline is non-obligatory, is regulated, and amenable to correction [8-11, 14].

CONCLUSION

Ideas akin to the concept of slow (non-obligatory) phenoptosis have helped to answer the question posed by Academician V. V. Frolkis: why do organisms consisting of potentially non-aging cell lines actually age? After all, their origins lie in tissue stem cells, and like cancer cells, these cells have no limit on the number of divisions. The renowned gerontologist Bernard Strehler (USA) also believed that there is nothing inherent in cells or multicellular organisms, that would prevent them from functioning without aging. But if the conditions necessary for such functioning are not met, cells inevitably begin to age.

For example, it was demonstrated [18, 19] that immortalized cells do not age under standard culturing conditions. Yet, under suboptimal conditions, even these normally non-aging cells can undergo rapid aging [20], as evidenced by the exponential increase in their mortality rate over time, consistent with the classic Gompertz law observed in humans and animals. In 2025, this law of mathematical thanatology celebrated its 200th anniversary and remains a fundamental tool for gerontologists and demographers alike.

Interestingly, it was also possible to create conditions under which normally non-aging hydras [21] begin to age, following the same classic Gompertz law with an exponential increase in mortality rate [22]. The mortality statistics across different countries, where populations live in diverse socio-economic, climatic, and other conditions, reveal patterns reminiscent of aging of hypothetically non-aging individuals [8]. Variations in conditions affect coordinated changes of both parameters of the Gompertz law, precisely following the trajectory away from the boundaries of stable life activity (non-aging zone) in the multidimensional space of the organismal states in response to demands imposed by the external environment [23].

In fact, the kinetic patterns of human aging [8, 24] closely mirror those observed in non-aging hydras under aging-inducing conditions. As civilization progresses, humans are increasingly removed from the pressure of natural environment and corresponding behaviors, moving further away from the non-aging zone. However, this shift occurs along with civilizational reduction in baseline mortality, which leads to the increase in the average life expectancy. At the same time, the likelihood of extreme longevity for individuals decreases due to the increase in the kinetic parameter of the Gompertz law, i.e., faster increase in the mortality rate with age. Nevertheless, both the average and maximum lifespans of laboratory nematodes have been increased several times by artificially minimizing both parameters (through hypomorphic mutation of the regulatory genes *daf-2* or *age-1*) [25, 26].

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Conflict of interest
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