ISSN 0006-2979, Biochemistry (Moscow), 2023, Vol. 88, No. 11, pp. 1683-1691 © The Author(s) 2023. This article is an open access publication.
Published in Russian in Biokhimiya, 2023, Vol. 88, No. 11, pp. 2038-2050.

REVIEW

"If I Were in Nature's Place, I Would Do It Like This..." Life and Hypotheses of Alexey Olovnikov

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Received July 12, 2023
Revised September 25, 2023
Accepted September 25, 2023

Abstract—In this article, we commemorate the life and scientific journey of the brilliant gerontologist-theorist Alexey Olovnikov (1936-2022). In 1971, he published his famous "marginotomy" hypothesis, in which he predicted the replicative shortening of telomeres and its role as a counter of cell divisions and biological age of an organism. This work put forth several remarkable assumptions, including the existence of telomerase, which were confirmed two decades later. Despite this, Alexey Olovnikov moved further in his theoretical studies of aging and proposed a series of new hypotheses that seem no less exotic than the marginotomy hypothesis once appeared. Alexey Olovnikov had an extraordinary way of looking at biological problems and, in addition to aging, authored striking concepts about development, biorhythms, and evolution.

DOI: 10.1134/S0006297923110019

Keywords: Olovnikov, marginotomy, telomeres, aging, printomeres, chronomeres

INTRODUCTION

In the international scientific community Alexey Matveyevich Olovnikov (1936-2022) is best known for his visionary work on telomere shortening and its role in aging (1971-1973) (Fig. 1). Colleagues knew him as an interesting conversationalist who was always concerned with unresolved problems of biology. Alexey could stir up the dullest seminar with his sharp questions. To his family and loved ones, he was a cheerful, gentle, undemanding person, curious about everything. But for everyone, his main trait was obvious – originality, which manifested in everything, from everyday routine (such as spreading documents on the floor because there was never enough space on the tables) to his life's work in theoretical biology, where his articles could be called anything but ordinary. Alexey also had a great love for terms and abbreviations, and in recognition of this we will give him his own abbreviation and further refer to him as AMO. In this article, we take a brief look at his scientific path, the history and evolution of the marginotomy theory, and more recent hypothesis explaining development, evolution, and aging.

Fig. 1. Alexey Matveyevich Olovnikov (1936-2022).

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Fig. 2. Alexey Olovnikov at the Gamaleya Institute (1960s).

BEGINNING OF THE SCIENTIFIC PATH. WORKS ON IMMUNOLOGY

AMO's scientific journey began when he studied at Lomonosov Moscow State University in the Department of Biochemistry within the Faculty of Biology, where he enrolled in 1953. During his university years, AMO became interested in immunology and entered the graduate program at the Gamaleya Research Institute of Epidemiology and Microbiology in the Department of Immunology and Oncology, under the guidance of Lev Zilber, a man of extraordinary accomplishments and hardships. Zilber was the creator of vaccines against the plague and other diseases, a pioneer in the discovery of cancer antigens, and one of the founders of the viral theory of cancer [1]. In the Gamaleya Institute, AMO worked on various topics of applied immunology (Fig. 2). His experimental work and Ph.D. thesis focused on the development of immunosorbents as tools for diagnostics and immunization. The list of publications for his thesis was decorated by an article in *Nature* co-authored with his supervisor, Aron Gurvich [2]. In this article they described a powerful enhancement of immunogenicity through covalent cross-linking of an antigen to an insoluble carrier during immunization of rabbits. From 1966 to 1969 a new immunochemical method called aggregate-hemagglutination was developed, which allowed for highly sensitive detection of soluble antigens. Among other uses, this method has been used to test for microbial toxins and the tumor marker alpha-fetoprotein [3-7]. AMO translated several books, including "The Integrity of the Body" by F. Burnet (1964) and "Comparative Immunology" by E. Cooper (1980) [8, 9]. In 1977, AMO became the group leader at the Institute of Chemical Physics, where he developed immunochemical methods and supervised graduate students. AMO's later years were spent working at the N. M. Emanuel Institute of Biochemical Physics.

AMO's interest in immunology persisted for a long time. In 1972, he proposed the mechanism "isotransposition of transgenes" to explain antibody diversity. This mechanism implied a combination of so-called "transgenes," numerous DNA segments that differ in sequence and are juxtaposed in a specific locus [10]. Formation of variable regions of antibodies from such sequences could result in an enormous number of variants depending on the number of transgenes encoded in the DNA. According to his hypothesis, recombination of the individual transgenes was expected to occur through a process called "extracopying," which involved creation of extrachromosomal copies of the individual transgenes that would combine into a coding gene. We now know that this is an intrachromosomal recombination process.

AMO's theoretical findings were ahead of their time but remained largely unnoticed because they were not published in accessible journals. AMO's immunological hypothesis was presented at the symposium "Molecular-Genetic Basis of Antibody Biosynthesis" in October 1972 in Tsaghkadzor, Armenia, and published in the "Problems of Immunology" by the Gamaleya Institute in 1974 [10]. About five years later, Susumu Tonegawa discovered that during the differentiation of B lymphocytes, the variable regions of heavy and light immunoglobulin chains are formed by combination of several segments, each represented in the immunoglobulin gene

locus in multiple different variants. This recombination creates antibody diversity. For this discovery, Tonegawa was awarded the Nobel Prize in Physiology or Medicine in 1987.

TELOMERE THEORY OF AGING

AMO's hypotheses were sometimes very complex, containing numerous additional constructions that could obscure the main idea. Despite the fact that the statements in his articles were supported by the published results, the logical conclusions were often so unusual, unexpected, and novel, that they were perceived as fantasies and even provoked rejection and protest. This was the case with the theory of terminal underreplication, or marginotomy (shortening of chromosome ends), first published in the Proceedings of the USSR Academy of Sciences in 1971 [11, 12]. It is AMO's most famous theoretical work. Surprisingly accurate predictions not only of the existence of the phenomenon itself, but also of the biological consequences arising from it, later aroused genuine interest, because they were made long before telomere shortening and its molecular mechanisms were discovered and studied.

The story of the discovery began in 1966 with a lecture by histologist Alexander Friedenstein, where AMO heard about the recently published data of Leonard Hayflick that normal somatic cells (fibroblasts) cannot divide indefinitely *in vitro*, and after about 50 doublings they stop [13]. Moreover, the cells have a program that counts doubling: after 20 divisions, Hayflick froze the cells in liquid nitrogen; upon thawing, the cells did 30 divisions. In other words, the cells "remembered" that they had already undergone 20 divisions and had only 30 left.

AMO said that this fact shook him so much that he could not think of anything else [14]. How could the cell division counting program be arranged? As always, a non-trivial explanation arose. Picturing how the replicative complex could work, AMO concluded that DNA cannot be replicated at the very end, and if so, with each doubling it would become shorter at its ends. Shortening DNA to a certain critical limit can lead to dysfunction of the genes near the telomere and cell death. The telomere theory of aging that was born then, explained the Hayflick limit by attributing the role of a timer that counts the number of cell divisions to telomere shortening.

Many predictions based on AMO's then entirely speculative hypothesis of marginotomy were confirmed. For example, the fact that the ends of telomeres are composed of a repeating buffer DNA sequence, which serves as a consumable, was experimentally established [15, 16]. The postulate about the existence of a specialized DNA polymerase, which compensates for the shortening of telomeres during germ and stem cells divisions, was also brilliantly confirmed [17, 18]. Because of this enzyme, the germ line does not age and ensures full transmission of the genetic information in an infinite number of generations. This specialized reverse transcriptase, called telomerase, was initially discovered in the ciliate Tetrahymena and characterized by Elizabeth Blackburn and Carol Greider [19].

In their article describing the history of telomerase discovery, Blackburn and Greider wrote that they were not aware of the Soviet scientist's hypothesis until 1988, when Calvin Harley drew their attention to this work [20, 21]. Intrigued by this hypothesis, Greider and Harley decided to test whether chromosomes shorten in human cells, and whether the process observed in *Tetrahymena* was a general biological phenomenon, as predicted by AMO [22]. From then, the number of studies on the terminal replication problem began to grow exponentially.

In addition to telomerase, AMO predicted that the mechanism designed by nature for germ line immortality also opens up the possibility for a pathology: a somatic cell can hijack telomerase and embark on a path of infinite proliferation [12]. Indeed, telomerase is activated in ~85% of cancers [23]. In the marginotomy theory, the ability of bacteria to undergo unlimited replication and their "immortality" was explained by the circular form of their chromosomes: since a circle has no ends, bacteria do not require the compensatory DNA polymerase. We now know about another way to protect telomeres. Drosophila lacks telomerase but extension of chromosome ends is carried out through the use of specialized mobile elements: retrotransposons that are capable of copying themselves via reverse transcription attach to the ends of chromosomes [24]. Several other assumptions were also made in AMO's hypothesis, including that "antimarginotomy" (i.e., telomere elongation) could have therapeutic applications. Last, but not least, AMO hypothesized that telomere shortening and the "death of cells participating in regulation of the activity of hypothalamus and of other homeostatic centres" are the primary cause of aging.

Above all, AMO was interested in the mechanisms of development and aging, genetic structure of the program that guides an organism throughout its ontogenetic journey from birth to death. Initially, the telomere theory ideally described the program of aging. However, over time, accumulating data suggested that the telomere theory worked for cultured cells but failed to explain aging of the whole organisms. For example, when comparing wild and laboratory mice, it was found that their telomere lengths differed significantly, with the telomeres of laboratory mice being up to 10 times longer [25]. It could be assumed that they should live longer than their counterparts in the wild, but they had the same lifespan. Telomerase-null mice were also bred, and they were fully viable, reproduced well despite the absence

of telomerase, and aged at similar rate to the others [26]. Only in the 4th or 5th generation did problems start to emerge, and the 6th generation turned out to be infertile. Also, within the same organism, mitotic counters in different tissues are not synchronous and allow for different numbers of duplications. No subtelomeric "aging signal" was found, and even in senescent cells, i.e., cells that had exhausted their division potential, the ends of chromosomes were consistently packed with telomere-binding proteins and protected from exonucleases. Despite the overall confirmation of the predictions of the telomere theory, AMO's hope that it would become a universal principle explaining the cause of aging of the organisms did not come true. According to him, telomere shortening is merely a witness, not the cause of aging [27].

Thus, the story came full circle: disappointed in marginotomy as an explanation for aging, AMO limited its application to explaining the "lifespan" of cell culture, which was the initial purpose of the hypothesis. It was necessary to find a new solution.

It should be noted that the role of telomeres in aging continues to be actively studied. For example, according to the recent findings, telomere dysfunction occurs in senescent cells, regardless of their length, and some researchers consider telomere damage to be an important checkpoint that triggers cell death [28, 29]. Furthermore, there is a telomere-centric theory, according to which many signs of aging, including mitochondrial dysfunction, activation of inflammation, chromatin structure disruption, and changes in proteostasis are activated through telomere dysfunction [30, 31]. The role of telomeres in aging is the subject of several articles in this issue, as well as a special memorial issue of *Biogerontology* titled "Telomeres in Health and Longevity".

Fig. 3. Alexey Olovnikov gives a talk at the gerontological conference (2000).

GENERAL THEORY OF DEVELOPMENT AND AGING

AMO was a proponent of programmed aging and was sure that this program has a specific genetic mechanism involving a limited set of factors, that nature easily regulates based on evolutionary and population needs. Having discovered a number of inconsistencies in his previous hypothesis, AMO further developed it to make it more universal [27, 32-34] (Fig. 3). The staples of the new aging theory can be summarized as follows: (i) marginotomy serves as a reliable counter of cell duplications; (ii) however, shortening of the chromosome ends does not play a fundamental role in organism aging; (iii) Vladimir Dilman's neuroendocrine theory of aging [35], which AMO considered central to explaining animal aging, must be taken into account, and (iv) aging is an integral stage of ontogenesis, and therefore there must exist a unified regulatory mechanism of development – from birth to death.

AMO proposed that maintenance of the cell in an active differentiated state and its aging are based on the shortening of special, still hypothetical, extrachromosomal linear DNA molecules that carry regulatory genes, and which are protected by telomeric repeats at their ends, similar to the linear chromosomes. He called these molecules printomeres – "prints" of specific chromosome regions [32-34]. Once copied from their chromosomal origin, tissue-specific printomeres function in dividing cells to determine and maintain the state of cellular specialization. AMO suggested that during the early stages of embryogenesis, when a brief morphogen exposure should determine the fate of a specific group of cells, creation of a printomere serves as a means to implement positional information. According to the hypothesis, printomeres encode small RNAs responsible for the expression of specific genes by decompacting certain chromatin regions [32, 36]. The hypothesis assumed strict positioning of the chromatin relative to the nuclear membrane. By binding to the complementary sites on the chromosome near the nuclear membrane, small RNAs can briefly open a nuclear pore (hence this type of RNA was called fRNA – fountain RNA). As a result of a rapid influx of ions from the perinuclear space into the nucleus in a strictly defined

location, decompaction of chromatin occurs, which activates a set of genes controlling a given cellular differentiation pathway. RNA-dependent ion regulation of chromatin may also be involved in the X-chromosome inactivation, gene position effect, and the phenomenon of genetic dominance. AMO hypothesized, "that eukaryotes "invented" the perinuclear cistern embracing the karyoplasm and chromosomes just to be capable of strictly local, targeted, ion-dependent manipulations of their chromatin database". Over time, the shortening of printomeres can lead to a decrease in the dosage of regulatory RNAs that maintain the necessary activity of chromosomal structural genes. However, AMO did not consider this hypothesis exhaustive, as it explained the activity and aging of individual differentiated cells and tissues but not the coordinated functioning of the entire organism.

According to Dilman's neuroendocrine theory, the central governing body (the "physiological top manager"), which in higher animals is the central nervous system (CNS), is responsible for directing development, organizing, and maintaining the balanced functioning of the entire organism, and determining its aging. Considering this work, AMO suggested that the neurons of the brain have their own printomeres, which he called "chronomeres", and which control the maturation and aging of the organism according to its biological age [27, 33, 37, 38]. In this revised theory, aging is now explained not by the shortening of telomeres *per se* but by the shortening of the ends of extrachromosomal DNA, thereby reducing the dosage of regulatory RNA required to maintain gene activity in the cells of a given type. More specifically, chronomeres control the expression of hormones and their receptors in the neuroendocrine and neurotrophic centers of the CNS. As a result, they regulate the diverse array of processes occurring in the organism. AMO referred to aging as a "disease of quantitative traits" caused by a decrease in gene activity following critical shortening of these extrachromosomal counters.

Another important point of the new hypothesis was that shortening of the chronomeres in post-mitotic neurons should occur in waves synchronized with infradian rhythms. AMO reached this conclusion based on the works of Walter Pierpaoli, who experimentally investigated the role of neuroendocrine organs, particularly the pineal gland, in the development and aging of animals [39, 40]. In his paper [37], AMO described in detail how he envisions this process. Most importantly, he came to the conclusion that the rhythms cannot be endogenous. All living creatures on Earth are subject to the external cyclic influences of geophysical nature that inevitably affect their life processes. Two hypotheses, published in 2005 and 2022, explore the influence of gravity, the most reliable and eternal rhythm driver on Earth, on development and aging [37, 41] (Fig. 4). These striking concepts of aging shift our gaze away from the microscope and remind us that we live on planet Earth, in its cosmic environment. For instance, the hypothesis published in 2005 postulated the existence of a physiological "lunasensor" located in the cells of the pineal gland (pinealocytes), which respond to the mechanical action of calcifications – the long-described "brain sand" – upon changes of lunar cycles and the gravitational influence of the moon [37]. This mechanism explains the sudden surges in hormone release, changes in developmental cycles, and other phenomena.

Fig. 4. Vladimir Skulachev, Alexey Olovnikov, and Vladimir Anisimov at the gerontological conference on the island of Stromboli (Italy), organized by Walter Pierpaoli (2005).

In his latest "metronome" hypothesis, AMO formulates a new view on the cause of aging, rejecting the existence of a special program, which he had been a supporter of throughout his career [41]. However, he could not deny the existence of a very specific physiological mechanism that measures biological time. Similar to the lunasensor hypothesis, the organism living on Earth is considered here as a target for the constant influence of powerful external geophysical forces. Such forces are periodic shifts of the Earth's axis, which lead to changes in the direction of the cerebrospinal fluid flow, perceived by the ciliated neurons of the brain ventricles (also a long-known type of cells). This, in turn, is proposed to trigger epigenetic mechanisms mediated by "temporal DNA" that affect development. Aging in this hypothesis is seen as a post-reproductive stage of development, when the main goal, the propagation of life, is achieved, and the temporal DNA is exhausted. How the lunasensor and metronome relate to each other remains unexplained. However, considering AMO's gift of scientific foresight, all of his hypotheses are worth investigating.

AMO's views have evolved throughout his career. The new general hypothesis, consisting of a range of concepts, was developed by AMO over many years, becoming more complex and incorporating various hypothetical mechanisms and new terms, becoming more difficult to understand [42]. However, it is worth noting once again that its fundamental principles are: (i) the existence of "paragenome", that is, temporary functional extrachromosomal DNA molecules, (ii) centralized regulation of developmental processes by the CNS, and (iii) the relentless influence of two timekeepers: internal molecular (marginotomy) and external geophysical. Each of these phenomena individually has a lot of experimental evidence.

EVOLUTIONARY THEORY

AMO's interests were not limited to aging, biorhythms, and ontogenesis. Like many biologists, he was haunted by the problem of limited choice for natural selection, since the percentage of randomly occurring favorable mutations is low. The insufficiency of random errors was noted by Darwin himself, and "since then – AMO writes – this old thorn still remains in the body of evolutionary theory" [43]. In organisms that find themselves in an unusual habitat, adaptive evolution can only be successful with timely and sufficient genomic variability. If mutations are the fuel for selection, then the mechanism that delivers this fuel in a timely manner is as important for evolution as natural selection. Crossing-over does not help here: blind gene shuffling does not create fundamentally new traits. AMO proposes a model of a specialized "evolutionary machine" ("creatron") [43, 44]. According to the hypothesis, in order to modify the germ cell genome in a targeted manner, i.e., to create non-random mutations, molecular signals must be delivered from the "exercising organ" (according to Lamarck) to the genome of germline cells. In the article [45], AMO offers an explanation for the mysterious fact well known to embryologists: the migration of primary germ cells through the developing embryo before settling into the gonads. He suggests that this happens to acquire tissue-specific markers by the primary germ cells, allowing the adult germ cells to become receptive to the molecular signals of those organs, which their predecessors (the primary germ cells) contacted during early organogenesis. According to the hypothesis, the relay interface that receives signals from the organs and redirects them to the gonads after processing is a neuronal projection of body parts in the brain, similar to the "Penfield's homunculus" [43-45]. The transneuronal signal delivery from a specific organ is targeted, meaning it is directed towards non-random groups of germ cells. Thus, the evolutionary machine should appear as a transmission of signals from an organ that functions abnormally due to changing conditions, to a neuronal projection in the brain, and from there to the gonads, where "tissue-specific" germ cells will receive the signal. The end result of this scheme is epigenetic modifications of the strictly defined loci in the genome of germ cells, that correspond to the "exercising" (stressed) organs. Topographically non-random epigenetic changes occur in the population and are transmitted to offspring *en masse*, resulting in a sharp increase in the frequency of beneficial changes in the descendants. Over several generations, epigenetic changes have an increased chance of becoming genetically fixed. Further development of the evolutionary theory is devoted to the problem of which molecule could be used as a signal for non-random genetic changes. In 2022, an expanded evolutionary hypothesis was published, discussing the possible role of stable circular RNAs that could serve as messengers from soma to gonads [43]. It is noteworthy that the publications on changes in the level of small RNAs in animal germ cells under the influence of environmental stress have appeared [46]. These changes are considered as the beginning of an adaptive process in the changed living conditions.

ALEXEY OLOVNIKOV'S APPROACH TO SCIENTIFIC PROBLEMS

Here we provide a brief and superficial overview of AMO's works. Not all of his ideas were published, although he carefully worked out each hypothesis. Typically, when faced with an unsolved problem, he would gather extensive literature on the subject and seemingly unrelated topics, engage in discussions with specialists, and at some point, all of this helped him to consider

Fig. 5. Alexey Olovnikov with his wife Natalia Olovnikova at the Demidov Prize ceremony (February 2010).

the problem from a broader perspective and identify the missing link within the context of the already known structural and functional organization of the biological process. AMO described his approach in an article about morphogenesis: "To see the entire ocean as a whole is possible only from a satellite from which one cannot see the waves but can clearly distinguish underwater currents and other oceanic mysteries. In this work, I attempted to rise as if on a satellite, realizing that it is simply impossible to review all the literature on morphogenesis, but it is interesting to try to take a fresh look at some of the still unsolved mysteries of this fascinating process and give them my own interpretation" [47].

AMO had the rare ability to see the unobvious and not be afraid to talk about it. Certainly not all of his conclusions and thoughts will be confirmed, however when it came to publication, he was always confident and even said that if he was in nature's place, he would do things exactly as he proposed. At the same time, he believed that it was easy to kill a nascent vulnerable hypothesis with criticism and destructive questions, so he carefully guarded new ideas for a while and did not share them with anyone. AMO's articles are overflowing with information because, in addition to the hypothesis, numerous corollaries with detailed explanations were placed there. It cannot be denied that AMO's articles are hard to read, they often tire or even irritate the reader with detailed hypotheses built upon hypotheses [42]. It is difficult to predict what will prove visionary in his articles or which of his ideas researchers will be motivated to test. But we want to emphasize once again that these hypotheses should also be considered from a higher perspective, extracting the key elements – the ideas and principles.

CONCLUSION

It must be acknowledged that AMO was very fortunate in that, despite the lack of active promotion, one of his predictions not only got experimental confirmation but also gave rise to a new scientific field, bringing him worldwide recognition. Telomere biology has remained at the forefront of science for several decades, and it seems that the discoveries in telomere regulation are endless (transcription of telomeric repeats, telomere signaling, telomere elongation by recombination, etc.). In 2009, AMO experienced the peak of his popularity when a group of scientists who discovered and studied telomerase received the Nobel Prize. AMO himself was among the scientists nominated for the prize, but was not awarded. Many wondered how he dealt with such a disappointment. However, to anyone who knew AMO closely, it was clear that his worldview did not involve resentment or disappointment. AMO wrote that he was pleased with confirmation of his hypothesis, and with having published it on time [21]. Having written this article in 1966, he published it only in 1971 in a Russian journal, and in 1973 in an international one. In the winter of 2010 AMO received the Demidov Prize, an honorary scientific award, established in 1831 (Fig. 5). In his inaugural lecture, AMO of course spoke about his main work, telomere shortening, taking lines from Alexander Pushkin's poem as an epigraph: "...The days slip by, and every hour takes away a bit of being from us".

Perhaps to some, AMO may have seemed strange, unusual, or even extravagant person. However, he was always very responsive and engaging when it came to science. He greatly valued freedom – freedom from dogma, schedules, and formalities. We sometimes use

the term "man of integrity", and AMO was the epitome for it. He was by no means an unworldly person, and loved his family, had an interest in everything – from politics to academic gossip – and at the same time, a joyful and clear light was always present in his life: his passion for science.

Contributions. N.I.O., I.A.O., A.I.K. writing and editing of the article.

Acknowledgments. Photo credit (Figs. 1 and 3): Sergey Novikov.

Ethics declarations. The authors declare no conflict of interests in financial or any other sphere. This article does not contain any studies with human participants or animals performed by any of the authors.

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