On the Immortal Hydra. Again

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Abstract—The long history of ideas about the most famous “immortal” (non-aging) organism, freshwater hydra, is shortly reviewed. Over the years this polyp has attracted the attention of naturalists interested in problems of aging and longevity. In recent years, this interest has abruptly increased with the accent on fine mechanisms providing an almost complete lack of aging in hydra. It is emphasized that hydra immortality is based on indefinite self-renewal capacity of its stem cells. It is this fact that allows the polyp to continuously replace the “outworn” cells of the organism, keeping all its characteristics unchanged for an almost unlimited time. It is concluded that the applicability of the data obtained in gerontological experiments on hydra to human being is, unfortunately; very limited because normal functioning of many important organs and tissues in highly developed organisms is determined by the presence of postmitotic cells (neurons, cardiomyocytes, etc.), which actually cannot be replaced.

Keywords: freshwater hydra, aging, life span, cell proliferation, evolution, stem cells.

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In January 2014, the journal *Nature* published an article [1] whose authors, using appropriate demographic data, compared the age-related changes in the force of mortality and fertility in 46 living creatures (11 mammals, 12 other vertebrates, 10 invertebrates, 12 vascular plants, and 1 green alga). The main conclusion of this study was that, in a number of species, the probability of death not only does not increase with age but may remain the same and sometimes even decrease. The theoretical calculations of the authors showed that a population of the freshwater hydra *Hydra magnipapillata* can survive without breeding for at least 1400 years, which allows it to be considered as virtually immortal. This study has caused a surge of publications in mass-media (newspapers, magazines, and online publications), whose meaning was boiled down to the fact that it is now clear where to search for the key to the abolition of aging in humans and that the same mechanisms that are used by hydra for “eternal” life can be adopted to the fight of humans for their own immortality. In this article, I would like to express my point of view on the “phenomenon of the immortal hydra,” which, unfortunately, is very different from the above.

However, at first we need to focus on some definitions. When we speak of immortality in a biological sense, we certainly do not speak of the organisms that cannot be killed in principle. Based on the classic definition of aging as a set of age-related changes (which, it should be noted, can consist in both accumulation and disappearance of something) that lead to an increase in the probability of death [2–7], we call immortal those organisms that do not grow old, whose probability of natural mortality is almost zero. Such organisms should not be confused with the non-aging ones that have a limited (sometimes very small) life span because the probability of their death is fairly high, although it does not change with time. Actually, that is why it follows from the data of [1] that even those species whose probability of death decreases with time (but remains high enough) have a much lower life span than hydra.

The freshwater hydra attracted the attention of scientists as early as in the middle of the 18th century [8, 9], 10–20 years before the birth of Mozart, as was rightly noted by Werner Müller in his article [10] devoted to the morphogenesis/structure formation in hydra. Already at that time, the enormous regenerative potential of this organism (a new individual may
develop from even one hundredth of the old one) was identified, and an assumption about its practical immortality was made. Later, the interest in hydra as a possible object of gerontological (and not only gerontological) studies repeatedly increased and decayed until the 1990s [11–15]. A particularly great contribution to the understanding of how the hydra’s organism functions was made by Belgian researcher Paul Brien, one of the most outstanding specialists of the 20th century in gametogenesis and blastogenesis [16–19].

It was found that the freshwater hydra, indeed, can avoid aging and, apparently, cancer. In certain circumstances, it does not have postmitotic and senescent cells at all. In such a situation, eliminating the necessity for sexual reproduction, it can live almost infinitely, multiplying by budding and having, as mentioned above, a vast regenerative potential. Apparently, hydra extricates itself from this situation as follows [17, 19–21]. It is believed that the so-called interstitial cells (or simply i-cells) of hydra can both be involved in the formation of buds and give rise to gametes. Gametogenesis in hydra occurs periodically, after which it could again start asexual reproduction. However, under certain conditions (e.g., ambient temperature change), gametogenesis is delayed, which leads to the depletion of the pool of i-cells, decrepitude, and eventual death. If this does not happen, i-cells can almost infinitely function as stem cells. The area of continuous growth in hydra is located under the hypostome. The newly formed cells move upwards (to the hypostome and tentacles), downwards (to the formed buds and sex glands), or over the body column to the basal disc, through the aboral pore of which necrotic masses are excreted. The size and individual characteristics of the polyp remain constant. Thus, hydra is constantly completely renewed, getting rid of the “outworn” cells.

Aging (see the definition above) must necessarily be accompanied by either accumulation or disappearance of something. By the way, the opposite is not necessarily true. For instance, in humans, the probability of death remains virtually unchanged until 14–15 years of age, although the body undergoes dramatic changes; however, they either do not affect the probability of death or even reduce it. In hydra, we can observe a steady state between these two processes. On the one hand, it always produces “outworn” cells, but they are constantly eliminated. On the other hand, its stem cells continuously provide an adequate replacement for such “waste.” Perhaps that is why hydra is called an “eternal embryo” in many articles (see, e.g., [22]).

A new wave of interest in hydra as an immortal organism arose after the publication in 1998 of the experimental work by Martínez [23], who analyzed the mortality and fertility in three cohorts of *Hydra vulgaris* for 4 years. In his experiments, hydra bred only by budding (though occasionally some individuals still produced sperm and eggs) and that produced offspring was immediately removed from the experimental population. It was found that, during the entire observation period, the force of mortality remained negligible, and the ability to reproduce did not change at all. The author concluded that his results confirm the long-existing hypothesis about the absence of aging in hydra and its potential immortality.

The article by Martínez led to the emergence of a number of works whose authors either attempted to cast doubt on his conclusions about the absence of aging in hydra [24] or were aimed at clarifying the possible fine molecular and genetic mechanisms that ensure the immortality of this organism (see, in particular, [25, 26]). The number of the latter has especially increased since 2010, when a large international team of researchers published data on a complete sequencing of the genome of *Hydra magnipapillata* [27]. The authors of some articles specifically emphasized the above-mentioned fact that, in some species of the genus *Hydra* (e.g., *Hydra oligactis*), a fairly rapid aging is still observed, which is caused by changes in ambient temperature, which, in turn, initiates sexual reproduction [22, 28, 29].

A large number of articles devoted to the problem of hydra immortality were published by a group of German researchers headed by Thomas Bosch [25, 26, 30–32]. In studying the molecular and genetic mechanisms that determine the unlimited ability of stem cells of hydra to self-renew, they concluded that the decisive role in this phenomenon is played by the transcription factor FoxO. Bosch and his co-workers performed a series of experiments on *Hydra vulgaris* and showed that the overexpression of *foxO* increased the intensity of proliferation of both interstitial and progenitor stem cells as well as activated stem cell genes in the terminally differentiated somatic cells. The downregulation of *foxO* led to an increase in the number of terminally differentiated cells and a drastic decrease in the growth rate of the polyp population. In addition, it led to the downregulation of stem cell genes and expression of the antibacterial peptide AMP. The authors concluded that these results testify to the evolutionarily conserved role of FoxO in the control of the life span in different organisms from hydra to man and shed light on the mechanisms of cell aging. They cited a number of studies whose results suggest that FoxO3A and FoxO1A gene polymorphism underlies longevity in humans [25]. Thus, Bosch and co-workers hypothesized that the FoxO gene affects the life span of humans by regulating the proliferative activity of stem cells and the terminal differentiation (as in hydra) [26].

Apparently, the ability of stem cells of hydra for constant self-renewal is really the key property that ensures the immortality of the polyp. However, in my opinion, the role of this factor in humans is very limited. Hydra, similarly to all other cnidarians, is a very
primitive representative of the animal world. Instead of the central nervous system, this polyp has only sensory and motor neurons, which are connected in a network via intermediate neurons and ganglia. It is only this system that determines the responses of hydra to external stimuli. It does not have cells that could not be replaced without any damage to the organism and that, at least to some degree, would determine its individuality. In contrast, in humans, a significant proportion of most important organs and tissues consists of postmitotic (neurons, cardiomyocytes, and erythrocytes) or very slowly dividing (hepatocytes and fibroblasts) cells. In many cases, they do not divide or are not replaced by new ones, not because the body does not have such opportunities but because these cells should not divide or be replaced. Otherwise, they will simply not be able to correctly perform their functions. By the way, many of our cells (e.g., skin fibroblasts) retain their mitotic potential (“according to Hayflick”) until an old age [33], without spending their telomeres during continuous reproduction. Of course, the stem cells do not have problems with telomerase; however, even the regeneration of the brain or the heart with the use of stem (satellite) cells can lead to disturbance of the required connections between neurons or cardiomyocytes in these highly complex systems. Apparently, this is our fee to evolution for high organization and intelligence.

In connection with this, the prospects for increasing the life expectancy of humans due to the manipulations with FoxO seem rather vague to me. This approach, apparently, can only reduce the viability of the human body due to the suppression of proliferation of stem cells and subsequent decrease in the regenerative potential. However, the converse, with the above mentioned in mind, seems very unlikely, because the stimulation of reproduction of stem cells that is not implied by our developmental program will not ensure, anyway, regeneration of, for example, neurons or cardiomyocytes. And even if it does, this may lead to unpredictable consequences, such as the aforementioned disturbances in the normal functioning of respective organs. The appearance of multiple benign tumors cannot be ruled out either.

According to the concept of aging that I hold, aging is just a byproduct of the program of development [2, 6, 20, 21, 34], whose implementation in higher organisms necessarily implies the appearance of cell populations with a very low or even zero proliferative activity; this, to some extent, determines the limited ability of relevant organs and tissues to regenerate. At the same time, it is the presence of such highly organized populations of highly differentiated cells, quite unable or partly able to reproduce, which ensures the normal functioning of the higher animals and humans.

However, there is reason to believe that the restriction of proliferation or replacement of cells forming tissues and organs of the vast majority of metazoans is the main reason of the accumulation in them of various stochastically arising macromolecular lesions [3, 6, 7, 19–21, 34–40]. The most important of the latter are the lesions in DNA (since the damage of the main template in many cases cannot be fixed), which subsequently, through a chain of different events, will lead to an increase in the probability of death of the body, i.e., to aging. The higher the proliferation rate of cells (or their replacement with the newly formed ones), the easier they should avoid the accumulation of such damage at the level of the entire cell population due to simple “dilution.” The hydra apparently ensures such a “dilution” through a continuous renewal of all cells, which allows it, under certain conditions, to maintain its viability unchanged for a practically unlimited time.

This concept is confirmed by the ample data obtained both by us and by other researchers using the model of the so-called “stationary phase aging”—the accumulation of “age-related” damage in cultured cells whose proliferation is somehow restricted (preferably by contact inhibition). It was found that, within the framework of this model system, changes similar to those observed in the cells of aging metazoans occur in these cultured cells, including the accumulation of single-strand DNA breaks and DNA-protein cross-links, DNA demethylation, changes in the level of spontaneous sister chromatid exchanges, formation of abnormalities in the cell nucleus structure, changes in the plasma membrane, deceleration of mitogen-stimulated cell proliferation, deterioration of the ability of cells to form colonies, changes in the dealkylase activity of cytochrome P-450, accumulation of the well-known biomarker of aging 8-oxo-2’-deoxyguanosine in DNA, increase in the number of cells with senescence-associated beta-galactosidase activity (the most commonly used biomarker of cellular aging), inhibition of poly(ADP-ribosyl)ation of chromatin proteins, etc. (for review, see [6, 7]).

Importantly, such experiments can be performed on most diverse cells, including both normal and transformed cells of animals and humans [41], bacteria, yeasts, plant cells, mycoplasmas, etc. This fact provides an evolutionary approach to the analysis of the results [42]. Furthermore, the “age-related” changes in cells of stationary cultures can be revealed fairly soon, usually in 2–3 weeks after the start of the experiment.

However, it should be noted that, at present, I have an impression that even the data obtained on such “essential” [39] models cannot be automatically extrapolated to the situation in the whole organism [3, 20, 21]. Thus, I would say that currently I hold an anti-reductionist standpoint [3, 21, 43, 44]. It cannot be ruled out that the process of aging of a multicellular organism is triggered at the whole-body level, although its implementation largely takes place at the level of individual cells. Therefore, the reduction of
the mechanisms that ensure an “eternal life” of the hydra to its simple continuous self-renewal at the expense of immortal stem cell lines can also be a reductionist simplification. However, today it seems unlikely to me that the data obtained in hydra gerontological studies can be easily extrapolated to humans.

REFERENCES


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