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Letter to Editor Open Access

Bioenergetics Aging Clock

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The theory of replicative senescence is based on the doubtless fact that cells of higher eukaryotes enter a non-dividing but viable state after a certain number of duplications, called the Hayflick limit. It is assumed that the accumulation of non-dividing cells in tissues leads finally to organism degradation [1], which is the leading cause of aging. The mechanism is that the ends of eukaryotic chromosomes have multiple repeating TTAGGG nucleotide sequences, called telomeres. They prevent end-to-end chromosome fusion and protect DNA from nuclease digestion. Telomeres are synthesized in embryonic cells by a special telomerase enzyme that is absent in most somatic cells. The telomeric chromosome ends of somatic cells become 50–200 nucleotides shorter with each division. As a result, after a certain number of duplications, the telomeric end is exhausted, and divisions cease due to chromosome erosion. This process is recognized as a mitotic clock [2]. This aging clock is obvious and convincing but is refuted now by many facts: the aging cells that exhibit telomerase activity have been discovered, plus potentially immortal tumor cells that lack telomerase activity were found. The mice zygotes that lacked the telomerase gene, but had full-size initial telomeric chromosome ends were obtained. The mice that developed from these zygotes proved to be viable and fertile. This initial length of telomeres was sufficient to support the normal viability of six generations [3]. At present, many researchers hold the opinion that the loss of telomeric ends actually results in chromosome erosion and death of a cell. However, the termination of the cell proliferation in the process of normal physiological aging takes place earlier than this critical moment. The telomeric apparatus cannot therefore serve as an aging clock, and is an additional barrier on the path to multiplication of malignantly transformed cells.

The neuroendocrine theory of aging developed by Dilman, under the name "The grand biological clock" has also been referred to as the aging clock theory [4]. Just as in a technical clock, the mechanism of time reckoning in this clock is based on rhythmic oscillations that are performed by a special oscillatory circuit. There are time (circadian) genes in each cell of all eukaryotic organisms. In vertebrates, they are active mostly in the suprachiasmatic hypothalamic nucleus. These genes express the proteins that inhibit their own transcription. Such systems with negative feedback produce auto oscillations because each unit of a system reacts to the signals of other units with some lag. The greater this lag, the larger the oscillation periods. The hypothalamic oscillatory circuit is adjusted so that its rhythms are close to the day illumination rhythms. The signals from these circadian rhythms are transmitted to the pineal gland (epiphysis), which secretes melatonin in beat with oscillations, with maximum secretion at dark times of day. The core destination of the suprachiasmatic oscillatory system is to change the melatonin production. The rhythmic fluctuations in the concentration of melatonin in the blood change the daily activity of most of the endocrine system, and, subsequently, the activity of many of the organism's systems. All empirical data indicate that the circadian clock machinery orchestrates organism metabolism to ensure that development, survival, and reproduction are attuned to diurnal environmental variations [5], but there is no reliable information on its role in the aging process. This is a physiological clock that generates cycles one after another, but does not sum results that is necessary to perform the role of aging clock.

Thus, there is no convincing mechanism of aging clock by now, but the new bioenergetics aging clock follows from the bioenergetics theory of aging [6] and some other empirical data as a logical consequence. This theory provides proofs that the harmful processes accompanying aging are caused by programmed bioenergetics decline. The genetic program controls the only function: decreases the bioenergetics level as cells divide. This increases the content of ROS in tissues, decreases the total level of protein synthesis and efficiency of the reparation mechanisms, causes tissues decrepitude (as result of cessation of cells dividing) and generates a number of other harmful processes. Each of these phenomena in turn entails a series of destructive processes, which form jointly an execution mechanism of the genetic program of aging that leads to the degradation of an organism up to the level incompatible with life. Aging is inherent not only to multicellular organisms, but also to the cells that are cultivated in vitro. Hayflick and Moorhead [7] noted in the conclusive part of their historic work on cell cultivation that the amount of cell divisions in a culture was only determined by internal factors, i.e., the number of duplications was programmed in each cell. This conclusion was drawn based on experiments in which the growth of a culture of fibroblast cells taken from human embryos was interrupted by freezing to -70°C for different periods. Independently of the duration of these periods and their number, the irreversible termination of proliferation took place after the summary passage of about 50 divisions. As mentioned, the bioenergetics theory of aging states that the termination of cell proliferation is caused by a decrease in bioenergetics levels until a certain threshold. Together with the Hayflick and Moorhead data, this leads to the conclusion that the level of cell bioenergetics is strictly related to the number of duplications elapsed. This provides grounds for concluding that the genetic program reduces a cell's bioenergetics level intermittently in the process of every round of mitosis. Consequently, a lifespan of cells is counted by bioenergetics clock. According to the chronologic clock, the lifespan of the fibroblast cells of a human embryo in a permanent culture is a little more than 600 days, but a section of the cells of the same culture, which have undergone freezing, live longer by the quiescence period. However, according to the bioenergetics aging clock, their lifespan is equal (50 divisions), i.e., the aging clock is not synchronized with the chronologic clock. The bioenergetics aging clock sets the rate of the cell bioenergetics degradation and consequently longevity. This clock is

capable to slow down or accelerate process of aging depending on environment conditions.

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