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SELECTED THEORIES OF AGEING

WYBRANE TEORIE STARZENIA SIĘ ORGANIZMÓW

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A – przygotowanie projektu badania | study design, **B –** zbieranie danych | data collection, **C –** analiza statystyczna | statistical analysis, **D –** interpretacja danych | interpretation of data, **E –** przygotowanie maszynopisu | manuscript preparation, **F –** opracowanie piśmiennictwa | literature review, **G –** pozyskanie funduszy | sourcing of funding

SUMMARY

Aging is a biological process, the mechanisms of which are not fully known to us. Therefore, there are many theories on the mechanisms governing it. This paper describes the four theories that provide information on the molecular aspects of aging of organisms. The first theory assumes the impact of telomere length on the length of life. Telomeres are nucleoprotein structures located at the ends of chromosomes, which protect against the loss of genetic information and which shorten with each cell cycle. Excessively shortened telomeres are conducive to the development of cancer, and aging of cells and organisms. The second, mitochondrial, theory describes the impact of accumulating mutations in the mtDNA on aging. According to this theory, the aging process is caused by free radicals, i.e. chemically reactive molecules, formed in the mitochondria of eukaryotic cells as the result of the reduction of molecular oxygen. The toxic effect of such reactive oxygen species leads to the accumulation of oxidative damage and malfunctioning of cells. According to the third, immunological, theory, the main cause of aging is decreased immune function and reduced amount of produced T and B lymphocytes and disturbances in the production of antibodies, all of which progress with age. According to the fourth, cell theory, homeostatic imbalance is the main cause of ageing. Aging of cells in the elderly causes them to be more prone to the so-called old-age diseases. Each of the described theories provides a better understanding of the extremely complex process that is ageing, even though they do not provide complete explanations of its mechanism.

KEYWORDS: theories of aging, mechanisms of aging, lifespan

STRESZCZENIE

Starzenie się jest złożonym procesem biologicznym, którego mechanizmy nie do końca są znane. Istnieje wiele teorii dotyczących mechanizmów tego procesu. W pracy opisano cztery teorie, które poruszają molekularny aspekt starzenia się organizmów. Jest to teoria telomerowa zakładająca wpływ długości telomerów na długość życia. Telomery to zlokalizowane na końcach chromosomów struktury nukleoproteinowe, chroniące przed utratą informacji genetycznej, ulegające skróceniu z każdym cyklem komórkowym. Nadmiernie skrócone telomery sprzyjają powstawaniu nowotworów, starzeniu się komórki i organizmów. Teoria mitochondrialna mówi o wpływie kumulujących się mutacji w mtDNA na procesy starzenia. Według niej za procesy starzenia odpowiedzialne są wolne rodniki powstające w mitochondriach komórek eukariotycznych w wyniku redukcji tlenu cząsteczkowego. Teoria immunologiczna za główną przyczynę starzenia uważa postępującą z wiekiem obniżoną czynność układu odpornościowego, zmniejszoną ilość powstających limfocytów T i B oraz zaburzenie produkcji przeciwciał. Teoria komórkowa w braku homeostazy upatruje główne przyczyny starzenia się organizmów. Starzenie komórkowe u osób w podeszłym wieku sprzyja zapadaniu na pewne typy chorób, nazywane starczymi. Każda z opisanych teorii umożliwia lepsze poznanie tego niezwykle złożonego procesu, jakim jest starzenie, choć nie wyjaśnia w pełni jego mechanizmów.

SŁOWA KLUCZOWE: teorie starzenia, mechanizmy starzenia, długość życia

Background

Ageing is a common biological process, which depends on a number of factors: genetic, environmental and random. It would seem that the genetic factors have the greatest effect, which can be supported by the relationship between the length of life and the species of the organism. Each organism living on Earth has a set of genes, which affect its metabolism, height and reproduction. However, there is no gene in the genome which would determine the length of life and ageing [1]. There are genes, though, participating in repairing DNA and ensuring homeostasis is stress conditions, which are said to affect longevity [2].

There are many theories of ageing and each strives to answer the question why and how we age. In this paper we discuss the telomere, mitochondrial, immunological and cell theories, which provide direct causes of ageing and describe its mechanisms [3].

Telomere Theory

Telomeres are DNA and protein structures located at the ends of chromosomes of eukaryotic cells. They safeguard the ends of chromosomes from degradation and loss of genetic information [4]. They are responsible for allowing the repair systems to determine which chromosome ends are good and which are damaged, for the spatial organisation of a nucleus and for the regulation of the transcription of genes located in subtelomere areas [5]. They prevent chromosome aberrations and ensure proper course of the recombination process [6].

The build and length of telomeres depends on the species, specimen, organ and even a single chromosome [7]. Human telomeres are composed of tandem repeats of the sequence (5'-TTAGGG-3')n in the double stranded cytosine-rich fragment of the DNA between 10 and 20 bp long and in the single stranded guanine-rich DNA between 50 and 300 nucleotide long [8]. In somatic cells, telomeres are shortened with each replication cycle. This phenomenon is the effect of the natural replication process of the end of the DNA [9]. The shorter the telomeres and the faster they are shortened, the faster a given organism ages [6]. The length of telomeres shortens with age, on average by 26 bp per year. Short telomeres are an indication of progressing ageing and can be interpreted as a signal to stop further cell division and apoptosis [10].

Each cell has a finite number of cell divisions, the so-called Hayflick limit, which affects the life span of a given organism. Telomeres act as "molecular clocks", an indicator of the critical value of the life span of a given cell. The Hayflick limit is characteristic for a given species and for a human being corresponds to ca. 80 divisions [11]. It is believed that the limited number of divisions and ageing of cells is a natural means for cells to prevent genetic instability. Lengthening of telomeres gives the cell more divisions, but also increases the risk of accumulating mutations which can lead to tumorigenesis [6].

Mitochondrial Theory

According to the mitochondrial theory of ageing, the ageing process is caused by free radicals. These highly chemically reactive molecules, usually found in cells, damage cellular components, which leads to impaired physiological function of cells and affects the progressing process of ageing [12]. The reactive oxygen species (ROS) are formed in mitochondria and therefore mitochondrion is the organelle which is the most susceptible to their effects. The noxious effects of the ROS lead to mutations in mtDNA and oxidative damage of other mitochondrial components. This damage impairs the working of the respiratory chain, which in turn leads to increased production of ROS and further mutagenesis [13]. Accumulation of mtDNA mutations causes the ageing of organisms. Lower mitochondrial function caused by impairment to the respiratory chain and lowered ATP production leads to cellular impairment and loss of function. These results are the most clearly visible in cells with high energy demands (nerve and muscle cells). An accumulation of mutated mtDNA molecules in somatic cells and lowered mitochondrial efficiency which can be observed with age corroborates this theory [3]. An accumulation of mtDNA mutations observed with age can also be caused by errors in replication and unsuccessful repairs of the DNA. Replication of mtDNA is independent of the cell cycle and unsuccessful repair of DNA. Errors made by mitochondrial DNA polymerase cause the accumulation of mutations, which surpasses the effectiveness of the repair systems. With age, the efficiency of mtDNA repair systems decreases substantially. Once the level of irreversible damage increases, despite the efforts of the repair systems, the mitoptosis (mitochondrial suicide) mechanism is activated [14].

Immunological Theory

According to this theory, the activity of the immune system deceases with age, which makes the organism more prone to infections and less efficient in destroying old and neoplastic cells, which leads to ageing and, eventually, death. This theory was developed by an American gerontologist, Roy Walford, who was considered a pioneer in biology and the medicine of ageing [15]. According to his hypothesis, the process of ageing of humans and other mammals is the result of incorrect immunological processes. Old-age diseases are very frequently the result of immune reaction regulation disorders and chronic inflammation [16]. According to the immunological theory, ageing is the result of malfunctions of the immune system, which is responsible for effectively combating antigens, i.e. destroying abnormal own cells and undesirable cells or foreign substances from the external environment.

The process of ageing is caused by changes in the development and biological function in most immune cells, which leads to unsuccessful destruction of changed own cells, decreased resilience to infections, and decreased effectiveness of vaccines. Some of the known changes (thymic atrophy, changes in the lymphocyte T composition) can limit the activity of immune cells to antigens of pathologically changed own cells [17–18].

Cell Theory

Ageing of cells is a complex process, comprised of many components. The first is the change of cellular morphology. Ageing cells grow and become more flat. This change is observed in case of both normal cells and neoplastic cells grown *in vitro*. Another indicator of cellular ageing is an increased activity of the lysosomal enzyme, beta-d-galactosidase. It is the best known and the most commonly used marker for cellular ageing [19]. Another change associated with ageing is increased cell granularity, which is probably associated with an increase in lysosome mass in aged cells [20]. Cellular ageing is accompanied by a number of changes associated with proteins which compose the cytoskeleton of the cells. During the ageing process, the β-actin and tubulin protein count changes [21].

Ageing is accompanied by demethylation of DNA, which can be observed in many types of cells and tissues. It was established that the level of demethylation decreases in cells grown *in vitro* and with the number of passages. Apart from DNA demethylation, the demethylation of certain genes, such as MYC and β-act gene, was established. The process of ageing also comprises of hypomethylation. Studies of fibroblasts showed, that ageing is accompanied by hypomethylation of certain genes, e.g. the p16INK4a gene. The profile of DNA methylation in aged fibroblasts was similar to that observed in the DNA of neoplastic cells [22].

DNA damage, which causes permanent activation of the response to damage track, leads to faster induction of the ageing processes. If repairing DNA is impossible, this track can lead to apoptosis (cell suicide), which is beneficial as it prevents overt proliferation and therefore prevents malignant transformation. Apoptosis also prevents transferring wrong genetic information to offspring cells. This process is therefore significant in maintaining the homeostasis of the organism. Homeostatic imbalance caused by proliferation or apoptosis can be associated with progressing ageing processes and tumorigenesis [1].

Conclusions

For many generations mankind dreamed of stopping the process of ageing, therefore it is not surprising that many scientific theories on the mechanisms of ageing exist. Each of these theories helps to better understand this incredibly complex biological phenomenon. In the future, better knowledge may allow humans to actually interfere and stop at least some indicators of ageing [23].

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