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Introductory Chapter: Recent Studies on Cellular Aging and Rejuvenation

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1. Introduction

Certain creatures possess the properties of eternal youth and deathlessness. These include *Turritopsis* (a species of small jellyfish) and planarians. Old *Turritopsis* starts a degeneration to transform into polyps and thereby achieves a perpetual life cycle [1]. The old cells contained in an old imago change into young cells when the imago transforms into a polyp. The polyp then starts to grow until it reaches the imago stage. As the *Turritopsis* can repeat this cycle forever, it can be considered to exist in a state of deathlessness. Planarians possess a special property of not growing older. They contain numerous stem cells throughout their bodies and every portion of their body can reproduce [2]. Planarians may therefore be an ageless organism. The property of agelessness is also present in humans. The case of Brooke Greenberg, an American woman who could not grow older after developing highlander syndrome, was the subject of a number of news reports in Japan a few years ago [3]. Moreover, there are several reported cases of female patients who developed highlander syndrome; however, the veracity of these reports is unclear, and the gene that causes the syndrome has not been elucidated. The development of highlander syndrome in human patients suggests that humans might possess the genes that enable the property of eternal youth.

The actualization of eternal youth is a long-held dream, and numerous studies have been performed to elucidate the mechanisms of aging and to achieve eternal youth. Consequently, recent studies have partially elucidated the process of aging and proposed several anti-aging or rejuvenation procedures; however, the studies are currently in the middle stage, and the key elements of the aging process have yet to be elucidated. The purpose of this chapter is to present an overview of the recent topics on cellular aging and rejuvenation to provide an outline of the content in this book. This chapter also complements the chapters that follow; in which researchers introduce topics related to aging and rejuvenation.

2. The mechanisms of cellular aging

2.1. Aging by telomere shortening

Cultured human cells become older through repeated cell division. Cells eventually stop dividing when they reach the critical passage number, the Hayflick limit [4]. Blackburn [5] and Greider discovered that the telomeres function as a clock by marking the passage of time in cells. The molecular mechanism of aging, which is described below [6–8], was elucidated through this discovery.

RNA primer is degraded and exchanged to DNA with DNA polymerase I followed by replication with DNA polymerase III. However, the RNA primer present at the terminal portion of telomeres cannot be exchanged to DNA. As a result, approximately 100 sequence bases are shortened in every replication. The shortening of telomeres acts as a fuse and decides the limit of cell division. The length limit (M1 period) in human fibroblasts is approximately 5 kb, but most cells in elderly humans do not reach the M1 period [9]. Moreover, mouse telomeres are of sufficient length, even in old mice, due to the expression of telomerase. Otherwise, cells in the M1 period can continue to undergo cell division by transforming with T antigen [10]. In such cells, the shortening of telomeres continues, and cell division is finally stopped again by the fusion of mutual terminals (the M2 period) or apoptosis. Telomeres are therefore protected from further shortening by a safe limit (the M1 period).

The pathway from telomere shortening to the cessation of cell division has also been elucidated [7]. A telomere is formed by both double-stranded DNA, which is made by repeated sequences (“TTAGGG” in the mammals), and single-strand DNA (G-tail) of similar sequences that exist at the terminal portion. A telomere has to construct the T-rope structure to avoid degradation by DNA degrading enzymes. This structure gives the first signal to initiate the progression of cell division. The shortening of telomeres causes the obstruction of the T-rope structure and signals certain proteins, including telomeric repeat-binding factor 2 (TRF2), AMP kinase and histone deacetylase, to delay or stop cell division. The detection of the signal by AMP kinase activates p53 and/or p21 proteins and inhibits the work of the cyclin-dependent kinase (CDK) complex. Finally, the inhibition of the CDK complex causes cell division to stop at the G₀ period, because CDK is a control switch that determines whether cell division should be promoted.

2.2. The effects of mitochondria on the aging process

Mitochondria also have a role in the aging process [11, 12]. Mitochondria produce ATP using the electron transport chain pathway where reactive oxygen species (hydrogen peroxide, hydroxyl radical and hydroperoxyl radical) are produced. Reactive oxygen species are often leaked through the mitochondrial inner membrane, damage DNA, proteins, and lipids. It has been confirmed by the experiments with nematodes [13] that reactive oxygen species promote aging. For instance, the mutation of the *mev-1* gene in nematodes was found to result in a shorter life span, because the gene disruption caused a defect in the electron transport chain and an increase in the level of reactive oxygen species. Conversely, a mutation of the *age-1*

gene in nematodes caused the enhancement of catalase activity which degraded hydrogen peroxide and resulted in a prolonged life span.

Recent studies have suggested an interaction between mitochondrial dysfunction and telomere shortening because of the following process [12, 14, 15]. The shortening of telomeres causes the activation of the p53 protein, the activation of which inhibits the activities of PGC-1 α and β , which induce the activation of mitochondria. This inhibition finally causes a decrease in many important mitochondrial activities and the progression of the aging process. On the contrary, an increase in the level of active oxygen species due to mitochondrial dysfunction often causes the oxidation of telomeres; the numerous guanine repeats on telomeres cause them to react easily with oxygen. In telomere DNA, oxidation disturbs the combination of TRF2 with telomere DNAs and the normal T-rope structure, which is the first signal that cell division cannot proceed. Thus, under high concentrations oxygen, the telomeres in human cells are rapidly shortened and cell growth is inhibited.

2.3. The factors promoting the aging process

Studies using both old cells (M1 period) and young cells (Low PDL) have suggested other causes of the aging. When cell fusion occurs between a young cell and an old cell from which the nucleus has been removed, the cell division of the fused cell is inhibited. However, when old cells that were previously treated with a protein synthesis inhibitor are used, growth is not inhibited. Moreover, when the cell membrane of old cells or mRNAs of cells stopped at the G₀ period, respectively, are injected into younger cells, cell division stops or DNA replication is inhibited. These results suggest that some proteins, mRNAs and/or cell membranes that are present in older cells gradually accumulate with every cell division and promote the aging process. The genes corresponding to such compounds have also been screened [16, 17]. Some genes (*gas*, *gadd*, *mot1*, and *hic-5*) have been cloned. Unfortunately, they were not the most important genes for controlling the aging process. Recently screening has been performed using RNA, and some promising genes have been identified [18, 19].

2.4. The genes associated with premature senility syndromes

Information that is important for elucidating the aging process in humans can be obtained from the genes that cause premature senility syndrome. Five types of helicases (RecQL1, BLM, WRN RecQL4/RTS, and RecQL5) that untangle DNA chains exist in humans. The change of the proteins to abnormal sequences causes premature senility syndromes [20]. Werner, Bloom, and Rothmund–Thomson syndromes are caused by abnormal structures of the WRN, BLM, and RecQL4/RT proteins, respectively. The WRN protein, which is related to the replication, restoration, transcription, and stabilization of DNA or telomeres, is remarkable. In the case of patients of Werner syndrome, the onset of symptoms occurs after patients stop growing at approximately 10 years of age. In Werner syndrome, the aging process advances much faster than in normal individuals. Patients show normal nerve and immune systems but possess unusual chromosomes. The WRN gene was expected to become a target of aging in normal individuals, because with the exception of the speed at which aging advances, the symptoms are similar to the normal aging process. However, WRN knockout mice do not show premature

senility syndrome, whereas WRN and TERC knockout mice do [21]. Further investigation is necessary to improve our understanding of the relationship between WRN and the aging process.

The other remarkable premature senility syndrome is Hutchinson–Gilford progeria syndrome (HGPS), which is caused by partial loss of the lamin A protein [22]. HGPS patients are normal at birth. HGPS develops at 6–18 months of age; the average life span of an HGPS patient is 13 years. Lamin A exists inside a nuclear membrane and supports the structure of the membrane. It is changed to a farnesylated version to perform nuclear translocation, and farnesylated lamin A is related to both the replication and transcription of DNA and signal transduction. The unusual farnesylated lamin A that is found in HGPS patients is called “progerin” [23]. Progerin accumulates and inhibits translocation, and the inhibition causes the aging of cells. In normal individuals, progerin gradually accumulates in the skin cells due to aging. Progerin is therefore a target of treatments to delay the aging process.

3. Realizing cellular rejuvenation

3.1. Rejuvenation by telomerase activation

In humans, although telomerase can make telomeres longer, most types of cells (including fibroblasts, pancreatic cells, and nerve cells) show very low telomerase activity [24]. In contrast, germ and cancer cells, which actively perform cell division, show high telomerase activity and long telomeres. This suggests that the cells may be rejuvenated if telomerase can be activated [25–27].

Studies on the fibroblasts and mice that express telomerase reverse transcriptase (TERT) gene by transformation have supported this hypothesis [28–30]. For example, a human OSMU36-T2 fibroblast showing high telomerase activity was obtained by transforming the TERT gene into an OSMU36 fibroblast. The telomere length and the telomerase activity of OSMU36-T2 were several times higher than those observed in OSMU36 fibroblast, and many characteristics including the cell size, growth rate, and gene expression were similar to those observed in young fibroblasts [28]. Moreover, the life span of a TERT knockout mouse, which was produced by Harvard University, was much shorter (only 6 months) than normal mice due to the rapid shortening of the telomeres. When telomerase was activated in the knockout mice, neurons were formed and rejuvenation was found in some portions [29, 30]. Thus, it may be possible to initiate cellular rejuvenation in individuals as well as cultured cells through the activation of telomerase.

Telomerase activity and telomere length are affected by lifestyle [31, 32]. Researchers at California University group examined the effects of food, exercise, and psychological stress on the telomere length in 35 males [31]. The members of one group continued to consume vegetables as a staple food, to perform adequate exercise and to decrease psychological stress through self-control for 5 years. As a result, their telomeres were longer than the members of the control group. Other researchers investigated the effects of exercise. The results suggested that the athletes who ran more than 40 km every day were 16 years younger in telomere length.

Moreover, telomerase can be activated by some chemical compounds, which are expected to have applications as rejuvenation drugs. For instance, the rate at which telomeres shorten is accelerated by high serum concentrations of cholesterol, because cholesterol hastens cell division. Thus, mononucleosis patients who continuously took statin (an anticholesteremic agent) showed higher telomerase activity and longer telomeres than the patients who did not take statin [33]. Several years ago, a compound named TA-65, which was isolated from the root of the *Hedysarum*, was screened as a telomerase activating compound [34], and the rejuvenation effect of TA-65 was examined in mice.

As telomerase activity can be controlled by lifestyle and some compounds, the enhancement of telomerase activity may become an effective treatment to promote cellular rejuvenation. However, the enhancement of telomerase activity may also cause the activation or induction of cancer cells, because high telomerase activity is one of the characteristics of cancer cells [35–37]. Further studies to determine whether the activation of telomerase can truly induce a rejuvenation condition without the risk of cancer cell activation will be necessary before it can be used in supplements and drugs.

3.2. Rejuvenation by antioxidants

Leucocytes secrete reactive oxygen species to protect against psychological stress in social life or physical stresses including atmospheric pollutants, UV, and viruses. The excessive production of reactive oxygen species promotes aging (as described in Section 2.2.). Although catalase, superoxide dismutase (SOD), and glutathione peroxidase can remove such reactive oxygen species in humans, catalase, and SOD activities gradually decrease due to aging. Thus, reactive oxygen species cannot be sufficiently removed in elderly individuals. In other words, the aging process can be delayed or remediated if the excessive production of reactive oxygen species is prevented.

Antioxidants, such as vitamins and polyphenols, are effective in removing active oxygen species, and their anti-aging effects have been studied for many years [38, 39]. The studies suggest that the oxidation of cultured cells can be inhibited by antioxidants and that mice that continuously took antioxidants showed lower oxidation and a longer life span than controls. Recent studies in humans, however, suggested that the anti-aging effects are doubtful. For example, in experiments in which healthy human subjects took β -carotene or vitamins for a long period of time, the ratio of depth was not decreased. Certain amounts or components of antioxidants may be required to make the effects of antioxidants prominent in humans.

3.3. Rejuvenation by anti-aging hormones

Anti-aging hormones have remarkable potential as anti-aging or rejuvenation treatments. There are several candidate compounds, including *klotho*, *sirtuin*, *Bach1*, *Clk-1*, and polyamines [40–46]. The *klotho* gene is mainly expressed in the nervous system to control the calcium concentration in blood; *klotho* works as a controller of homeostasis, although the precise work of the protein has not been sufficiently elucidated [40, 41]. *Klotho* knockout mice develop many symptoms related to aging, such as arteriosclerosis, osteoporosis, motor

impairment and have a shortened life span. Conversely, *klotho* knock-in mice have a life span that is several years longer [42]. Thus, *klotho* is a promising target in rejuvenation.

Histone deacetylases (sirtuin) is another candidate protein [43, 44]. Sirtuin works as an energy economizing hormone to prolong the life span. Sirtuin 1, 6 and 7 knockout mice showed faster aging and a shorter life span. Hibernation, which represents a state of extreme energy limitation, extended the life spans of yeasts, nematodes, and mice. One reason for the prolongation of the life span is that the amount of excess active oxygen is decreased by the energy limitation; thus, the promotion of the aging process by undesirable oxidation is inhibited. Another cause is the activity of sirtuin. Sirtuin 2 is activated by the decrease of NAD, which is caused by energy limitation. The activation of sirtuin 2 increases the deacetylation of histones to silence the genes, and the economizing of energy prolongs life span.

The following monkey experiments were performed to estimate the action of sirtuin in relation to energy limitation. The Wisconsin National Primate Research Center examined the effects of calorie restriction on 76 rhesus monkeys. The monkeys that had been fed low-calorie food (a 30% calorie reduction) looked much younger and showed a longer life span than control members (100% calorie) [47]. However, a similar experiment by the NIA in the United States in 2012 suggested the reverse results [48]. Therefore, further discussion is necessary to confirm the relationship between anti-aging and energy limitation.

Resveratrol has been screened as a compound that is effective for enhancing the expression of the sirtuin gene [49]. When resveratrol was given to mice that had been fed a high-calorie diet, some of the factors of aging were inhibited, and the activities of AMPK and PGC-1 α were enhanced; however, the anti-aging effects were insufficient. If compounds that can more effectively enhance the sirtuin gene are discovered, they will become a prominent anti-aging hormone.

Polyamines also show remarkable characteristics. Polyamines, such as spermine, spermidine, and putrescine, are essential for the growth of mammals and play important roles in cell division and differentiation; however, their precise action has not been sufficiently elucidated [50, 51]. In most cells of the human body, the concentrations are maintained at low levels. They are only found at high levels in cells that are actively working, such as testicular cells and cancer cells. The amounts of polyamines in those cells are especially increased before DNA synthesis; the growth rate in cancer cells increases in proportion to the amount of polyamine that is added to the medium. Polyamines are therefore related to the activation of cells.

Some studies suggest that polyamines function as an anti-aging hormone. The addition of polyamines to fibroblasts enhanced the expression of genes related to aging [20], and mice that were contentiously fed a diet containing a high concentration of polyamine appeared much younger and had a longer life span than mice that were fed a diet without polyamine [52]. Other researchers, who had studied the relationship between *Lactobacillus bifidus* and life span, suggested that the life span of mice was prolonged by the polyamines that were produced by *L. bifidus* cells [53, 54]. The amounts of spermine and spermidine in humans gradually decrease due to aging, and the concentration of polyamines in the blood can easily be increased by eating foods, such as soy beans. Thus, polyamines may also be useful as supplements for anti-aging or rejuvenation.

4. Conclusion

In this chapter, the author focused on cellular aging and rejuvenation. Recent studies have gradually elucidated the aging process and have suggested that telomerase, the mitochondria and other components (RNAs and proteins) are involved in the aging process. However, these studies are ongoing. Moreover, studies on the aging process have identified several anti-aging compounds that can activate telomerase (TA-65), inactivate reactive oxygen species (anti-oxidants) and work as anti-aging hormones (klotho, sirtuin, resveratrol, and polyamine). In the near future, these compounds and/or other compounds with greater effects may become prominent drugs for anti-aging and rejuvenation.

Research into regeneration with the use of iPS cells is recently showing remarkable progress. Although the topic was not introduced in this chapter, the regeneration of cutaneous and nerve tissues or internal organs using regeneration medicine will be another means of realizing rejuvenation. Researchers studying anti-aging will have to watch the progress of both regeneration medicine and cellular rejuvenation research.

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