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The Mechanism of ROS Treatment in Long-Lived Animals

Eunsol Cho
Zhe Jiang Zhu Ji Rong Huai School, China
Grade 12

Abstract**—** *Long-lived animals, like humans, are produced ROS in mitochondria. In mitochondria, longevity animals first prefer the metabolism of reducing ROS production. Then, they have various gene groups that rapidly remove the generated ROS. DNA damage occurs when ROS is released into the cytoplasm and attacks DNA in the nuclear envelope. Even though weak DNA damage, cell apoptosis pathways are activated and repair pathways are suppressed in longevity animals*

If the repair path is activated by light damage, it would lead to carcinogenesis by neglecting the mutation. Longevity animals efficiently treat ROS from metabolic processes and induce the activity of genes involved in apoptosis even in nuclear DNA damage. Longevity animals rapidly remove mutagenic cells through the cell death pathway to create an environment for cell neoplasia and to minimize cellular senescence as much as possible.

Keywords**—** *Aging and Longevity, Life Span, Reactive Oxygen Species (ROS), DNA Damage, Long-Lived Species, Apoptosis*.

I. INTRODUCTION

Life expectancy at birth has been increasing for most of the last century in western societies, thanks to the continuous amelioration of medical assistance, to the improvement of the environment (in particular clean, safe water and food), and to the improvement of nutrients [1]. In a global country, The research on successful aging and longevity is underway in order to reduce medical burden correlated to the continuous increase of lifespan and the consequent grow of the elderly population. One of the main questions in this field is the correlation between the genetic background and lifestyle in determining the individual chance of a delayed aging and longevity [1].

Scientists suggests that an important indicator of life span could be genes, and that certain genes would offer protection from common age-related diseases like cancer, dementia and cardiovascular disease[3]. A person's life span is largely determined by the combined effects of genetics and environmental factors. Lifestyle choices, particularly diet, exercise and smoking habits, play an undisputed role in determining not only how long one will live, but also how well one ages. Genetic factors can contribute to the degree of longevity in at least two important ways: An individual may inherit certain genetic variations that predispose him or her to disease that decreases longevity; other gene variants may confer disease resistance [4]. Genetics is fundamental in EL (Exceptional Longevity), but it's not the only thing. So there may be other factors like environment or other lifestyles that may help people live longer and healthier lives. Future biotechnology would guide us to novel way to improve quality of life through increasing the chance to attain longevity by modulating the basic molecular mechanisms of aging. The aim of this review is to find out the biological and biochemical mechanisms involved in the aging process, and to seek the knowledge of the genetic basis modulating longevity may give significant hints on modulating lifestyle in order to attain longevity and extend healthspan [2].

II. HINTS FROM VERTEBRATE ANIMALS

Greenland sharks: The Greenland shark (*Somniosus* microcephalus) is the only shark that lives year-round in the Arctic and is the second largest carnivorous shark in the world [7]. Greenland sharks typically inhabit deep and extremely cold waters, thus they could conceivably colonize much of the world's deep seas [5]. The average size of Greenland shark ranges from 4 to 5 m, but specimens over 6.4 m and weighing over 1,022 kg have been recorded [7]. This species prefers cold water, between 0.6 and 12 ^{0}C, and depths greater than 200 m. During winter, Greenland shark is common in surface waters in estuaries, shallow bays, and coastal areas, but will move into deeper, cooler waters during the summer [5]. Greenland sharks live for hundreds of years, while the more than 5 meter long Greenland shark is one of the world's largest sharks, it is also one of the least understood animals on our planet [9]. But, marine biologists made a performance. to unveil one of the greatest of the mysteries surrounding this enigmatic shark, and showed an amazing revelation with a life expectancy of at least 272 years through carbon-14 dating [5]. The Greenland shark has the longest life expectancy of all vertebrate animals known to science [6]. The sharks' eyes have hidden the main clue to their life expectancy all along [7]. Lifespan study is based on the carbon-14 dating of Greenland shark eye lenses [8]. Greenland sharks are among the largest carnivorous sharks on the planet [9]. The production of free radicals such as Reactive oxygen species (ROS) might be responsible for cell senescence because free radicals can damage vital biomolecules like proteins, lipids and nucleic acids, causing cell senescence. Species longevity is linked to oxidative stress. Oxidative stress is a determinant of maximum species lifespan [11]. ROS, inevitable byproducts of aerobic metabolism, are known to cause oxidative damage to cells and molecules. Some studies show that long-lived species are more resistant to oxidative damage than short-lived species, and that long-lived species have lower antioxidant levels than short-lived species because they produce less free radicals [10]. It will be important to collect data on other metrics of oxidative status (e.g., DNA damage and repair) that

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might reveal routes through which Greenland sharks pave the way to their exceptional longevity. Hence, the oxidative status of the Greenland shark might have been shaped to some degree by adaptation to a life in the cold Arctic waters and to deep dives. For example, many species that are faced with repeated episodes of hypoxia/reoxygenation (as typical of diving animals) tend to have high basal levels of antioxidant defences in order to protect them against high free radical production that occurs during reoxygenation [10]. This might be one reason that explains why Greenland sharks have high antioxidant enzymes as compared to the other species.

Animals strive to maintain a constant redox state by balancing two counteracting systems, the radical-scavenging and the radical generating systems. Oxidative stress is created when this balance is disturbed either by the depletion of antioxidants or through an increase of oxidants [12]. Excess oxidative activity causes oxidative damage which includes peroxidation of lipids, protein carbonylation and formation of 8hydroxyguanines (DNA damage) [14].

The Bowhead Whale

The bowhead whale (*Balaena mysticetus)* live in Arctic and sub-Arctic waters, can grow to 20 meters in length and up to 100 tons in weight. The bowhead whale (*Balaena mysticetus*) is estimated to live over 200 years [13]. The cellular, molecular, and genetic mechanisms underlying longevity and resistance to age-related diseases in bowhead whales are unknown, but it is clear that, in order to live so long, these animals must possess preventative mechanisms against cancer, immunosenescence, and neurodegenerative, cardiovascular, and metabolic diseases [13]. A study suggest possible that these animals may possess genes associated with DNA repair, anti-aging, and effective antitumor mechanisms [13]. Low temperature in invertebrates in general, is associated with an overall slower life history, including slower growth rates at lower temperatures which may contribute to their exceptional longevity [15]. Lower temperature promotes longevity by slowing down the rate of reaction of various metabolic processes which affect development and life history. A lower temperature may also reduce damage that is the result of by-products of metabolism such as reactive oxygen species (ROS) [15].

Bowhead whale has unique amino acid changes and rapidly evolving genes which may contribute to slow aging over longevity [16].

Scientists suspect that Bowhead whales have superior anti-tumour mechanisms that are not present in humans [17]. The rationale goes like this: if cancer is caused by rogue cell dividing uncontrollably, then large animals like whales, which have over 1,000 times more cells than humans, must have a much higher probability of developing cancer and thus should be relatively short-lived [35]. Only they are not—some species can live up to 200 years—and therefore must have additional or more efficient mechanism(s) to protect them against cancer [17]. It need to identify candidate genes to explain the bowhead's higher life expectancy and disease resistance, including genes associated with DNA repair, cell cycle regulation, cancer and ageing [17],

It follows that larger, longer-lived animals must have an increased risk of cancer, compared to smaller, shorter-lived animals [18].

From the genome of other shorter-lived mammals Scientists could discover genetic differences unique to the bowhead whale[13]. It is thought that large mammals, such as bowhead whales, with over 1000 times more cells than humans, have a lower risk of developing cancer, suggesting that these creatures have natural mechanisms that can suppress disease more effectively than those of other animals [13]. Changes in genetic sequencing of the bowhead whale that related to cell division, DNA repair, cancer resistance, disease and ageing would provide novel findings to humans in order to fight age-related diseases [13]. The absence of tumors in marine mammals which contained lower concentrations of toxic chemicals suggests feeding, metabolic, or susceptibility differences among species, and genetic differences [21].

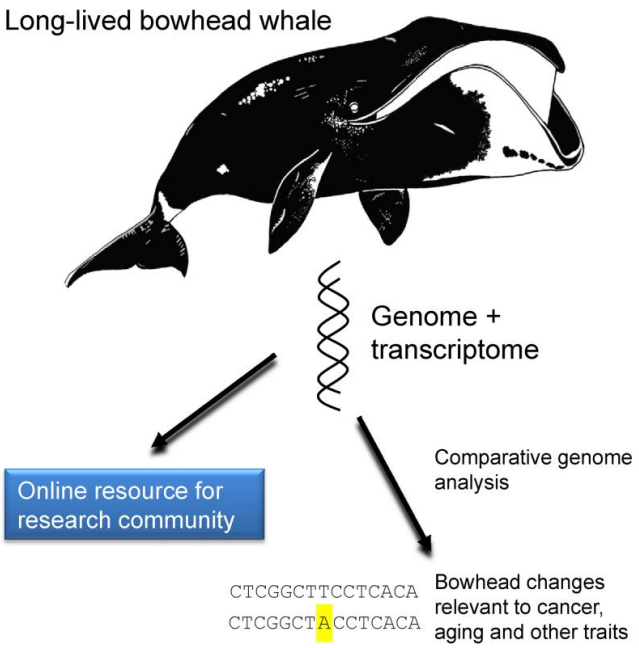

Fig. 1.

Elephants

Large body sizes in animals is an increased risk of developing cancer [22]. Animals with long lifespans have more time to accumulate cancer-causing mutations than organisms with shorter lifespans, and an increased risk of developing cancer [22]. Therefore, It should be observed a decrease in the copy number of oncogenes, an increase in the copy number of tumor suppressor genes, reduced metabolic rates leading to decreased free radical production, and increased immune surveillance in long lived animals such as elephants [22].

Elephants have 38 additional modified copies (alleles) of a gene that encodes p53, a well-defined tumor suppressor, as compared to humans, who have only two. Further, elephants may have a more robust mechanism for killing damaged cells that are at risk for becoming cancerous. Elephants have been long considered a walking conundrum. Because they have 100

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times as many cells as people, they should be 100 times more likely to have a cell slip into a cancerous state and trigger the disease over their long life span of 50 to 70 years [19]. One Asian elephant lived to 86 years in the Taipei Zoo [20]. A study shows that the African elephant genome has at least 40 copies of genes that code for p53, a protein well known for its cancer-inhibiting properties [19]. The results show that elephants have extra copies of a gene that encodes a well-defined tumor suppressor, p53. Further, elephants may have a more robust mechanism for killing damaged cells that are at risk for becoming cancerous. The findings could lead to new strategies for treating cancer in people [22].

Elephant cells have an enhanced response to DNA-damage that is mediated by a hyperactive TP53 signaling pathway, and enhanced cancer resistance in the elephant lineage evolved at least in part through reinforcing the anti-cancer mechanisms of the major 'guardian of the genome' TP53 [22]. Retrogene of the master tumor suppressor TP53 is essential for preventing cancer because it triggers proliferative arrest and apoptosis in response to a variety of stresses such as DNA damage [22]. The *TP53* retrogenes may functionally increase elephant cell response to DNA damage by triggering p53-dependent apoptosis rather than increasing DNA repair [23]. Apoptosis can prevent mutations from propagating to future cell generations through removal of mutated clones. The elephant cells appeared twice as sensitive to DNA damage–induced apoptosis as human cells [23]. Typically, introns are removed after a gene has been transcribed into messenger RNA but before it is translated into a protein. However, all but one of the *TP53* genes in elephants lacked true introns. This indicates that the 19 extra *TP53* genes likely originated when an edited RNA molecule, which had had its introns removed, was converted back to DNA [24].

III. ROS Role in Apoptosis

Apoptosis and cancer are opposed phenomena, but ROS have been widely reported to play a key role in both [27]. Although apoptosis and cancer represent opposite entities, ROS play an important role in both of the processes. Induction of cancer is clearly linked to oxidative DNA damage. Cells with DNA damage react rapidly to biological responses, including cell cycle arrest, initiation of DNA repair pathway, or apoptosis pathway. p21 arrests cells by affecting the activity of cyclin D-,E-,and A-dependent kinases, which regulate progression through the G1 phase of the cell cycle and initiation of DNA synthesis [33]. It is a target gene of the tumor suppressor p53 (2) and a key mediator of p53-induced G1 arrest in response to DNA damage

These events are likely to determine whether a cell will apoptose or survive and proliferate [27]. Many tumours are associated with inhibition of apoptosis through p53 mutations. H2O2 promotes apoptosis through conversion in HO· radical that directly attacks DNA or damages mitochondria. Reactive oxygen species (ROS) and mitochondria play an important role in apoptosis induction under both physiologic and pathologic conditions. Interestingly, mitochondria are both source and target of ROS. Cytochrome *c* release from mitochondria, that triggers caspase activation, appears to be largely mediated by direct or indirect ROS action. On the other hand, ROS have also anti-apoptotic effects. Apoptosis, or programmed cell death, has an essential role in controlling cell number in many developmental and physiological settings and in chemotherapy-induced tumour-cell killing. It is a genetically regulated biological process, guided by the ratio of proapoptotic and anti-apoptotic proteins. Recently, inducers of apoptosis have been used in cancer therapy. Several studies have attempted to induce apoptosis by triggering the tumour-necrosis-factor-related apoptosis-inducing ligand receptor and the BCL2 family of proteins, and others have targeted the caspases, and proteins that inhibit apoptosis. Most of these therapies are still in preclinical development because of their low efficacy and susceptibility to drug resistance, but some of them have shown promising results. Apoptosis can be induced by extracellular or intracellular signals and is conducted through two major pathways: mitochondrial (intrinsic) or death receptor pathway (extrinsic). Extrinsic pathway of apoptosis is triggered by interaction of death receptor and its ligand in cellular plasma membrane, which activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and generation of ROS [28]. ROS are well known triggers of intrinsic apoptotic pathway through interaction with outer mitochondrial membrane proteins. The intrinsic apoptotic pathway regulates the apoptotic cascades by the convergence of the signaling at the mitochondrion, such as those mediated by the Bcl-2 family of proteins. Once the outer mitochondrial membrane was disrupted, a set of proteins between the inner and outer mitochondrial membranes became active and promoted cytochrome c release [29]. The activated intrinsic pathway was crucial in initiating apoptotic cell death under the influence of ROS [29]. The released cytochrome c forms a cytochrome c/apoptotic protease activating factor 1/caspase-9 apoptosome complex, as recruited during apoptosis progression and included Bax and the initiator caspase-9 [29], [31]. Subsequently, caspase-3 and -7 was activated, causing the activation of caspase-3 downstream substrates which are critical to apoptosis [29], [31]. The cytochrome c release from mitochondria is controlled by Bcl-2 families [30]. Bcl-2 protein functions as an anti-apoptotic molecular rheostat that prevents cytochrome c release into the cytosol by a variety of apoptotic stimuli [30]. ROS was capable of functioning as an initial mediator in the p53-dependent mitochondrial apoptotic pathway. These results also support the notion that ROS serves a primary role in triggering apoptosis by activating the intrinsic pathway [29]. p53 is a transcription factor that not only induces growth arrest through transcription of the genes such as p21 and p27 but also triggers apoptotic signals via the induction of apoptosis-related genes [30]. The p53-induced apoptosis may be involved in the activation mitochondrial pathway through the elevation of ROS generation. The intrinsic (mitochondria-mediated) pathway is activated by cytotoxic stressors, such as DNA damage, radiation, growth factor withdrawal, and heat. Such stimuli are known to cause mitochondrial outer membrane permeabilization and stimulate the release of cytochrome c, second mitochondria-derived activator of caspase, where they work together to activate the initiator procaspase-9 within the

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apoptotic protease-activating factor-1. Once activated, caspase-9 activates effector procaspase-3 or-7, which, in turn, can cleave various protein substrates, leading to the morphological and biochemical features of apoptosis [32]. The p53 tumor suppressor protein can trigger the onset either of reversible or permanent growth arrest or of apoptosis [34]. p53 phosphorylation by different kinases in response to stress can select for arrest or apoptosis. p53 mutants can induce growth arrest but not apoptosis, or vice versa[34]. The p53 gene mutations may cause selective loss of the ability to transactivate certain p53-responsive promoters [34]. The role of the p53 tumor suppressor in tumorigenesis was thought to be restricted to its ability to activate certain cell cycle checkpoints and trigger apoptosis in response to cellular stress [38]. p53 is a tumor suppressor that regulates cell cycle progression and the programmed cell death response to DNA damage [37]. Loss of wild-type p53 function contributes to cancer development. p53 activity is lost through mutation in most human cancers. Loss of DNA-binding domain of the p53 result in a failure to activate gene expression. This leads to the loss of p53's normal functions, including the ability to inhibit proliferation or induce cell death. The mutant p53 may be important in the generation of a more aggressive and invasive tumor [36].

IV. ROS IN MITOCHONDRIA

Oxygen metabolism in the mitochondria Continuously occurs. Here, ROS is generated. As the amount of oxygen metabolism increases, the amount of ROS increases. There is not only one mitochondria in one cell. There are a number of mitochondria in one cell. Mitochondria also have their DNA. ROS is produced during the production of ATP in one mitochondria, but antioxidants are also produced to eliminate it. If enough antioxidants are not produced to remove all of ROS, the mitochondria begin to experience oxidative stress. The stronger the intensity of oxidative stress, the greater the mitochondrial DNA damage. At the same time, ROS is released into the cytoplasm through the mitochondrial inner membrane and the outer membrane, which attacks the DNA in the nuclear membrane. When nuclear DNA damage begins, the DNA repair path is activated. A cell suicide pathway must be activated immediately if it is irreparable damage. If the cell suicide path is not activated In time, the damaged DNA could not produce a cancer-suppressing protein, thus allowing cancer. The important thing here is mitochondria. To maintainin the normal function of mitochondria for long life is the key. Many scientists are now looking for a gene for longevity that is involved in normal mitochondrial function. Mitochondria are the first and most affected by active oxygen. There is a gene region that makes antioxidants in mitochondria. When mitochondrial genomic regions that produce antioxidants are attacked by ROS, mitochondrial DNA is damaged. Here, the mitochondria immediately disintegrate and a new mitochondria must be created. Cell senescence occurs when mitochondrial DNA damage is not disintegrated and remains intact. Some researchers have found that there is a gene that detects Mt DNA damage, dismisses the mitochondria and induces the production of new mitochondria. This is also a kind of longevity gene.

V. DISCUSSION

Longevity animals also breathe oxygen. Generation of ROS cannot be avoided. They also develop aging according to time. The thing to note here is to understand the concept of aging. Unlike cancer cells, the proliferation of normal cells is limited. The noncoding part of the end of the chromosome is called telomere. Once you proliferate, the length of the telomere decreases slightly. The reduction in telomere length is a sign of cellular aging. Cell senescence refers to a state in which the cell cycle is stopped. As the cell divides repeatedly, the length of the telomere is reduced to reach the critical point, cell division ceases. That is, the cell cycle stays at G1. This cell cycle arrest is irreversible. Cells with cell cycle arrest weaken their inherent cellular function. Aging cells with cell cycle arrest show strong resistance to apoptosis against external stress. Even if DNA damage is caused by ROS, apoptosis does not occur. This causes cancer. The smaller the number of aging cells, the lower the Probability of cancer. In order to avoid cancer, the cell should be converted to apoptosis by sensitively reacting to external stress such as ROS before the cell cycle is stopped. It is possible to guess that the number of senescent cells among longevity animals is relatively smaller than that of humans. It could be deduced that longevity animals have two characteristics over ROS. One is to reduce the production of ROS as much as possible, the rest is to produces a variety of antioxidants. However, It is hard to say that longevity animals could live long because they have excellent ability to respond to ROS. It should also be able to defend against viruses. We suspect that instant cell death on DNA damage is the secret of longevity. The activity of the p53 gene, which directs cell death, is the greatest feature of longevity animals.

TABLE I. Characteristics of cell metabolism on longevity animal and human.

Biomarker	**Human**	**Longevity Animal**
ROS	much	little
Antioxidant	little	much
p53 isoforms	little	much
Senescence Cells	much	little
Apoptosis	little	much

VI. CONCLUSION

Humans these days live pretty long lives, The average global life expectancy of someone born in 2015 is 71.4 years. That's not bad compared with some adult animal, which live for under 20 years. Over sponges, People don't know that sponges are animals. Some of them are very long-lived animals. Sponge longevity are often in the thousands of years. One study show that sponge from the species Monorhaphis chuni lived to be 11,000 years old. As far as mammals go, bowhead whales seem to have longevity over 200 years. It makes sense, since the marine mammals live in chilly waters. A cold environment causes a low body temperature, which in turn means slow metabolism—and thus less damage to tissues. For longevity, we should consider a therapy that induce late metabolism. Late metabolism reduces ROS, and it decreases

Eunsol Cho, "The mechanism of ROS treatment in long-lived animals," *International Research Journal of Advanced Engineering and Science*, Volume 2, Issue 4, pp. 176-180, 2017.

the possibility of DNA damage. Even though the DNA damage occur, induction of rapid apoptosis, could block the possibility of carcinogenesis due to mutation. Men could live up to 100 years through a therapy that induces apoptosis by detecting DNA damage in advance.

VII. Reference

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