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Mechanisms Underlying the Exceptional Longevity of Turtles

Lige Shang

Faculty of Science, The University of Sydney, Sydney, Australia
slgrigo7536@gmail.com

Abstract. Turtles are long-lived and are of great research relevance because of their extreme longevity, aging, and resistance to cancer. Numerous physiological hypotheses have been put forward such as low metabolic rate, antioxidant defenses, low baseline inflammation as well as tolerance to hypoxia but such factors are not exclusive to turtles and are unlikely to produce lifespan extremes singularly. It is a literature research synthesis in which it outlines the published evidence related to genomics and physiological findings and suggests a genome-maintenance-focused model of turtle longevity. It dwells upon the DNA repair programs and DNA damage response (DDR), tertiary programs that involve p53 control to explain how long-lived turtles can reduce the mutation rate and maintain genome stability during extended time periods. It also incorporates physiological characteristics as the reduction of damage input (persistent load and discrete peaks) which might supplement DNA repair as well as DDR. In general, this review places genome maintenance in relation to organism-level physiology in order to offer a consistent explanation of turtle longevity and insignificant senescence, as well as provide a comparative viewpoint of aging and cancer studies.

Keywords: Turtle longevity, Genome stability, DNA repair, Oxidative stress, Metabolic adaptations

1. Introduction

One of the vertebrates with the longest life span is turtles. Galapagos giant tortoises (Rana plateau) and Aldebar giant tortoises (Rana naine) may be suitable as an example of extreme longevity because some species can live more than a century [1]. They exhibit certain features such as extreme longevity and insignificant senescence [2]. Negligible senescence means practically no physiological castration, where mortality rates remain constant, reproduction remains unchanged and only minimal levels of functional impairment due to age [2]. As an illustration, the turtles of Blanding are a typical example of negligible senescence many studies have demonstrated that the turtles show abnormally low actuarial aging [2]. The models of aging under different environments of turtles give comparative values and their numerous biochemical mechanisms are analogous to those of humans. Therefore, evolutionary and biomedical implications of researching the turtles and characteristics of that animal present significance and give high values to the longevity of human species [1].

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Numerous mechanisms have already been suggested but are not complete yet [3]. The existence of some longevity mechanisms in turtles is not limited to the turtles, as the mechanisms are present in other animals. Namely, some of the mechanisms proposed involve low metabolism rates that retard ROS, high antioxidant capacity, which removes the free radicals, slow cell proliferation that minimized damage to replication, low inflammation that minimized the damage of immune and special physiological adjustments like hypoxia tolerance [3]. Nevertheless, these properties cannot be completely used to explain the extreme lifespan of turtles, though it is supported by evidence [3].

Recently genomic reports have indicated that the turtles possess certain mechanisms of genome maintenance [1]. First, turtles develop increased capacity in DNA repair [4]. Genomic and cellular research, in long-lived turtles, indicates an increase in repairs of DNA [4]. With the increase in lifespan, the damage of DNA increases, hence the long-lived animals require robust DNA repair. Second, there is an amplification of p53 pathway [5]. It triggers the arrest of cell cycle; the protector of the genome is the p53. Some of the long-lived animals like elephants have an increased or magnified DNA repair activity, and apoptosis during DNA damage and the p53 pathway [5]. Long-lasting species also have a more faithful monitoring system of DNA, and p53 is the major control factor. Third, a robust reaction in terms of DNA damage response is exhibited by turtles [6]. The ROS, UV, replication errors and environmental toxins damage DNA each day. Since damage to DNA is inevitable, species with long lifespan need the most efficient mechanisms. The DDR has the capacity to mediate and block such processes as pathways of DNA repair, cell cycle controls, apoptosis, senescence, and all of them are closely correlated to aging [7]. Longevity is closely related to all the above findings and such characteristics of genomic level also reflect in other long-lived species.

It is however still unclear how a combination of these physiological and biochemical mechanisms explains the enormously long-life span of turtles and how through this paper we can discuss the role of DNA repair in promoting longevity in turtles, how the processes of DNA repair works and how we can also include other factors like metabolism, antioxidant defenses and inflammation to explain such extreme long lifespan of turtles [3]. These mechanisms prove useful to know the longevity mechanisms, to foster more comprehensive context of aging and cancer research, and to give theoretical background to the further research. The analysis of the DNA repair, DDR and p53 will be conducted in the first part of the paper. The second part integrates the other physiological processes and it is followed by a close-up part in which the conclusions are summarized.

2. DNA repair mechanisms in turtles

The DNA repair could be one of the key processes contributing to the lifespan of turtles, and this section will consider four key techniques used to repair DNA and will explain how the process of DNA repair may be maximized in turtles to minimize the accumulation of mutations [4]. The loss of DNA damages takes place in a steady fashion and the unaddressed damages might build up as mutations in the DNA [7]. Overloading of DNA damage may result in numerous dangers such as deteriorations of cellular functioning, risk of cancer, and deterioration of cell stability. These dangers promote aging and ultimately, they result in death [7]. The DNA repair ability of turtle is very high such that the DNA damage repairs in time and minimizes the damage accumulation [4]. This increased repair ability minimizes these dangers and indirectly helps in the survival of the turtles. As such, DNA healing should be especially relevant to the longevity of turtles.

Four general DNA repair pathways are recognized such as the base excision repair (BER), nucleotide excision repair (NER), homologous recombination (HR), and non-homologous end joining (NHEJ). BER is mainly used to repair broken bases or to bend the DNA helix: particularly

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the problem of single base, which is oxidized, deoxidized, or alkylated [7]. BER determines the base that has been damaged, removes it, fills the gap, replaces the damaged strand with the correct nucleotide and, lastly, seals the DNA strand. Long-term genetic stability in organism exposed to oxidative damages can be achieved with efficient BER low mutation burden, and a long-lived organism that is susceptible to oxidative damage can utilize efficient BER. NER mends large sized DNA holes particularly photoproducts caused by UV light [7]. NER removes a small fragment of damaged DNA, and then, a re-synthesis with subsequent ligation of DNA happens. In the case of animals that are long-term exposed to the sun or to the chemical substance, NER helps to avoid long-term residency of the structural damage and reduces the risks of replication or transcription failures and cancellation. HR mostly fixes double-strand breaks (DSBs) and other dangerous damage, and is commonly referred to as a high-fidelity repair technique [6]. The most important characteristic of HR is homologous templates used to control repair as sister chromatids (similar to template-gioded repair). Since DSB is the most this type of DNA damage so an effective HR can eliminate chromosomal rearrangements as well as damage to critical genes and thus maintain the stability of tissues and reduce the chance of cancer over a long period. NHEJ also fixes the DSBs of DNA, but cannot depend on the presence of the homologous template, as well as compared to HR. NHEJ is a fast repair mechanism that can be mutagenic hence regarded as an error-prone repair mechanism [6]. When making a choice between efficiency and accuracy of repairs, the long-lived animals must balance between the choice. To illustrate, not only does it effectively seal the gaps so that the cells would not die, but it also reduces the level of errors through regulation.

Thus, whole-genome sequencing and comparative analyses on long-lived turtles have also reported some genetic modifications in the genes implicated in DNA repair and genome maintenance. In one of the analyses, it was suggested that certain genes relating to the repairing of DNA, maintenance of the genome, and tumor suppression have undergone expansion, duplication, or enrichment [1]. The other examination proposed the copying of anti-aging or DNA restoration-related genes, and also, longevity related cellular phenotypes, including resistance to stress and upkeep cellular balance [4]. Therefore, gene proliferation or duplication may result into gene dosage, consequently raising the total output of the associated protein since the number of genetic families has now enhanced and repair components are less depleted that induce repair is prompt and efficient.

Some of the damages that turtles incur throughout their lifespan include ROS and exposure to UV, replication-related damage, and environmental stresses. This damage puts repair as significant and time consuming. Thus, they have a high repair potential in terms of DNA. Nonetheless, it takes a system to investigate, slow down and control, i.e., DDR to be repaired.

3. Genome stability and DDR regulation in turtles

The process of DNA repair is not an independent process as the cells must first have to discover the damage and then make an appropriate response. Thus, the long-lasting turtles will probably have an integrated regulatory mechanism to control the integrity of their genome and regulate the restoration time and success. In this part, it will present the DDR as a surveillance-and-decision network, which comprises the connection between damage sensing and downstream responses such as repair, checkpoint control, senescence, or apoptosis, and it will comment on how DDR-regulated response can potentially prevent juvenile turtles, as well as DNA damage repair [7].

Overall, sensors detect DNA lesions and the signal is amplified, which then triggers the checkpoints and interactions to repair [7]. In case of the cases of mild damage, the cell cycle may stop and repair the damaged genome; in case of severe or chronic damage, the cell may undergo

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either senescence or apoptosis to deny the potential spread of mutations. This reasoning is particularly significant in regard to long-term species, as minor mistakes have to be prevented to continue over decades in order to slow down the process of accumulation of mutations and have the genome remain stable.

The results of the DDR need central regulator, which is p53. p53 can be called a guardian of the genome. Replication of damaged DNA is one of the most harmful to the cells. P53, in turn, triggers the cell-cycle arrest, which gives the cell time to repair DNA, which is analogous to activation of checkpoints [7]. p53 does not only activate a cell arrest, but also permits the cells to enter a priority repair mode, that is, promote the repairing of the DNA. It further enhances p53-stimulated apoptosis or senescence in case the damage can no longer be fixed [7]. Such functions make p53 a longevity tumor suppressor. To balance between genome stability and tissue capability to regenerate, longevity is essential. Thus, the improved control of p53 enables the damaged cells to be prevented to expand with lesions, slow the rise of mutation, and takes part to the stability of the genome and the decline of cancer, though it should be regulated by suitable means. It was reported through an analysis that mechanisms involving p53 are increased in certain long-lived animals, like elephants, and are linked to an increased capacity of DDR or tumor suppression [5].

Being one of the centers of the DDR, p53 balances the level of genome stability and thus extreme longevity or slower rates of aging [5]. This has been linked to the reduction of mutation accumulations, preserved tissue activity, and low risk of cancer which all lead to long life and slower senescence. Physiological functions have the capacity to decrease the input of damage whereas DDR signaling and DNA repair decreases damage processing. Genomic stability however does not just depend on the efficiency of repair and monitoring but also the load caused by the damage taken on DNA. Thus, the following section is going to touch upon how the metabolism, the oxidative stress, the inflammation and the adaptation to hypoxia affect the damage input and longevity of turtles along with the DDR and DNA repair pathways [3].

4. Physiological mechanisms that reduce damage input

DNA repair or DDR, is a central event in longevity; it processes the damage primarily. Nevertheless, lifespan is also determined by the rate of damage creation or burden of damage [3]. Therefore, it is significant to speak about which physiological processes can lessen the burden of the damage and cooperate with the DNA repair and DDR.

There are numerous physiological characteristics that can support the lives of turtles through decreasing the input of damage. One of the common ones is low metabolic rate, which might lower the activity of mitochondria and the total generation of reactive oxygen species (ROS). Oxidative stress is less probable to happen in the case of ROS level control, and it is likely that fewer oxidative lesions may be produced on DNA. In this regard, low metabolic rate might be considered a system to diminish the constant damage load that might indirectly diminish the long-term stresses imposed on DNA repair and DDR [3,8].

Inflammation of the baseline can as well be applicable even to the longevity of turtles. Long-term chronic inflammatory signaling is capable of enhancing oxidative and nitrosative stress and can establish a pro-damage environment in the long run, commonly referred to as inflammaging [9]. In the long run, assuming that turtles have relatively low inflammatory activity, the body can experience less persistent molecular stress, and the demands on the maintenance systems of the genome can be minimized. Thus, the inflammation level can be described as low, which is another kind of mechanism, which primarily reduces the input of persistent damage.

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Moreover, hypoxia tolerance has the ability to extend the lifespan of turtles because of other causes than reduced metabolism or reduced inflammation. Whereas low metabolic rate and low baseline inflammation primarily decrease the continuous input of damage, hypoxia tolerance can particularly benefit climbers in eliminating episodic damage spikes. Much of it is because many turtles, particularly aquatic ones, are adapted to endure the extended hypoxia, or even anoxia, in part by lowering metabolic rate (by reducing ATP usage) and shifting to anaerobic metabolism [10]. The oxidative stress in the process of reoxygenation may ensue and can cause transient surges of ROS, which at unregulated levels may augment oxidative lesions of DNA and augment the burden of harm [10]. Therefore, the hypoxia tolerance is important as turtles seem to contain the oxidative damaging spikes during reoxygenation, and this spike-control ability may be able to augment DNA repair and DDR to preserve genome integrity across long periods of time.

Such physiological pathways decrease the amount of damage and DNA repair and DDR fix the remaining damage, which increases longevity in turtles physiologically. This synergy is more realistic than a one-mechanism but it is elevated that the reduction of damage input without effective repair still permits residual profanity to accumulate whereas a more powerful repair with less damage load would be relentlessly damaged during extended life periods. A decrease in inputs of damage and an enhancement of the efficiency of DNA repair or DDR are both correlated, and result in the decrease of mutation buildup and genome instability, and an escalation of tissue homeostasis. In such a way, they promote long germ or high levels of longevity and low levels of senescence, i.e., reduced aging rate [2,3,8-10].

5. Conclusion

In general, this review provides evidence synthesis in explaining why turtles exhibit very long and low senescence rates using a framework based on genome maintenance. The presence of respective DNA repair pathways and DDR/p53-mediated regulation is significant, since it can process DNA lesions and eliminating them prior to fixation in the form of mutations is required to guarantee long-term genome stability in long lifespans. Nevertheless, longevity is also dictated by the rate at which the damage is repaired, but also on the amount of damage being generated daily. In this way physiological characteristics including low metabolism, antioxidant defenses, low inflammatory baseline, and hypoxia stress tolerance might play a role by decreasing the amount of damage and decreasing the total damage burden. In another dimension, hypoxia tolerance can be particularly relevant as ROS bursts could be present even during reoxygenation, and thus, by regulating these short-term empennulations, amounting to acute spikes, short-term oxidative lesions of DNA can be mitigated and the pressure on genome-maintenance machinery relieved. Thus coordination can be more important in causing turtles to live long: physiology reduces constant stress and peaks of episodic stress, and DNA repair and DDR determine the kind of response (repair, arrest, senescence, or apoptosis) that cells take to prevent the propagation of mutations and maintain tissue homeostasis. There are also wider implications to this integrated view, in that stronger genome maintenance can serve to constrain genome instability, and may be one part of the explanation of cancer resistance in long-lived species. Simultaneously, most recent results are predominantly founded on comparative genomics or correlational patterns hence the fact remains that genomic signatures have yet to be interconnected with functional outcomes. It is possible to directly test the DNA repair and DDR signaling dynamics in turtle cells during oxidative stress, hypoxiaestablished and hypoxiareoxygenation stresses to compare its efficacy in the short and long-term to determine the mechanisms by which this might be elucidated on a more functional scale.

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