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Keeping up with the Immortal Jellyfish: Biological Immortality in Animals and Humans

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ABSTRACT

Biological immortality is the state in which organisms do not die of old age or the natural and inevitable breakdown of cells over time. Although biological immortality is not currently the reality in humans, as our rate of mortality increases as we age, interestingly enough, biological immortality has been observed throughout the animal kingdom in organisms including the *Hydra* flatworm, *Turritopsis dohrnii* jellyfish, lobsters, and tardigrades. To achieve the shared goal of biological immortality, however, the aforementioned organisms employ various different mechanisms ranging from controlling FoxO gene expression to reversibly halting metabolism. The following paper overviews this variety of mechanisms and attempts to apply them to humans in order to evaluate the question: "Is it possible for humans to become biologically immortal?"

Introduction

If you were to ask someone what they were most afraid of, what would they say? Likely, many would name death as their fear. In the annual "Survey of American Fears," 29% of all Americans were identified as "afraid" or "very afraid" of dying while 58.1% specifically feared a loved one dying (1). Throughout the course of human history, death's position in life trajectories has consistently shifted; The human lifespan has evolved drastically, doubling over the past 200 years and 10 generations (2) to reach an average life expectancy of 73.5 years for men and 79.3 years for women (3). In fact, life expectancy continues to increase approximately 5 hours per day in developed countries (9). The maximum human lifespan is currently projected to theoretically range between 120-150 years (4) In comparison, humans' closest relatives, chimpanzees, have a life expectancy of 13 years at birth and maximum lifespan of <50 years (2).

The human lifespan has doubled over the past 200 years and consequently, has deviated from the lifespans of our closest neighbors in the animal kingdom, due to modern advancements in medicine such as vaccinations, improvements in hygiene and sanitation through modern plumbing and sewage systems, and increased access to plentiful and nutritious foods (3). These aforementioned improvements have yielded a J-shaped mortality curve for most mammalian populations, including humans, by minimizing mortality rates in early age and accelerating mortality rates only at older ages (3).

With improved control over environmental influences on human lifespan in the past 200 years, interest has grown in how modern science can now increase lifespan through understanding and regulating biological mechanisms. Biological immortality, thus, is defined as the state in which the rate of mortality does not accelerate as the organism ages since the organism is able to control or prevent the natural breakdown of cellular function over time. Research into biological immortality is a continuously developing field as the causes of aging are poorly understood. There are currently over 300 theories seeking to explain aging, ranging from genetic explanations which link longevity to the expression of a select key genes, to programmed theories of aging that hypothesize cells as having predetermined lifespans, and to error theories that describe aging as the product of unpredictable and random cellular damage accumulation over time (5). Lately, however, researchers have made notable strides into understanding biological

immortality by investigating the secrets behind the select instances of biologically immortal species in the animal kingdom. This review aims to examine these biologically immortal species and the intrinsic mechanisms protecting them against death from old age.

Methods

Peer-reviewed, published literature was identified through the Google Scholar and PubMed databases. Searches were made through combinations of the following key words: “biological immortality,” “senescence,” “aging,” “telomerase,” “FoxO,” “cryptobiosis,” and “stem cells.” Papers considered were generally published between 2003 to 2022. Because of the limited literature on biological immortality, one chosen study was published in 1998. Many publications chosen were studies focusing on one specific biologically immortal species and the experimental data used to identify the mechanism for longevity. Any information related to extrinsic causes of aging rather than intrinsic or biological factors were excluded. Relevant Google articles clarifying biological processes and molecules mentioned by the scientific literature were also included.

Results

Lobsters and Telomerase

The first organism of interest in biological immortality studies is the lobster. Technically, lobsters are not immortal in the sense that they can live forever in the absence of environmental pressures. On average, lobsters are estimated to live 45 to 50 years in the wild. However, what defines lobsters as nearly biologically immortal is that they do not display the typical signs of senescence or biological aging. Unlike the aforementioned J-shaped mortality curve exhibited by most mammalian populations, lobsters do not weaken or lose fertility with age, but instead grow indeterminately. Lobsters can also uniquely regenerate their limbs, indicating an advanced ability of cellular repair and division. (6).

The unique lifelong capacity of lobsters to continuously proliferate their cells has been linked to ubiquitous telomerase expression. Examination of lobster tissue samples had revealed high telomerase activity in all lobster organs (7). Telomeres are repeating DNA sequences that serve as protective “end caps” for chromosomes. As DNA is replicated, and cells divide to create new copies of themselves, telomeres shorten, eventually becoming so short that DNA replication and cell division is no longer possible (8). The Hayflick limit is the set number of cell divisions that can occur before the telomeres become too short for the cell to divide again (9). When the Hayflick limit is reached, cells are unable to replace themselves with new cells when they get damaged and age. Eventually cells die, and consequently, so does the organism. Telomerase is the enzyme that pushes back the Hayflick limit by regenerating and repairing shortening telomeres, which opens the door to infinite cell division (8). Thus, the infinite supply of telomerase in lobsters equips them with prolonged cellular lifespans that delay biological aging. This data is consistent with the telomere theory of aging, which emphasizes telomere shortening as the molecular clock that triggers aging and the importance of telomerase in sustaining lifespan through an endless ability to repair DNA (5).

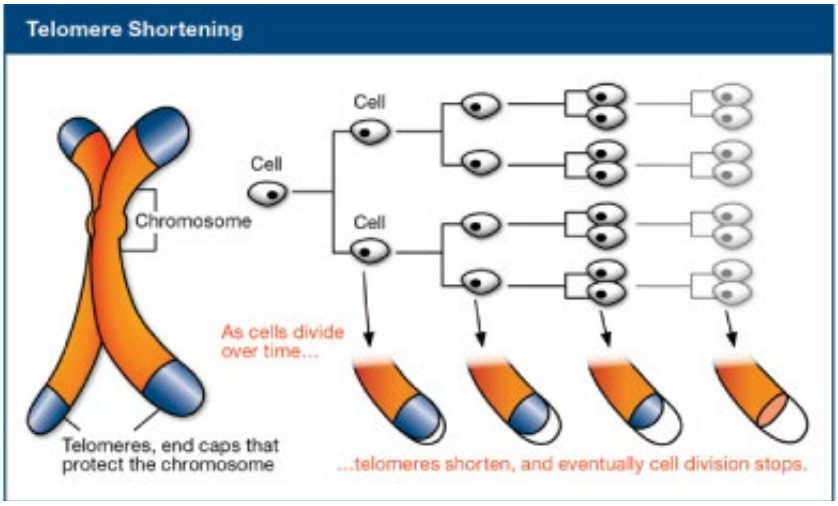

Figure 1 (10)

The question then becomes, is telomerase the pathway through which humans can become biologically immortal? Telomerase is not unique to lobsters; it is produced in many other organisms including humans (8). However, the key difference in the lifespans of lobsters versus these other organisms lies in the varying levels and durations of telomerase expression. In humans and most other mammals, telomerase is highly expressed during the embryonic life stage when cell division is fundamental to the development of a complex, multicellular organism from a single-celled zygote. However, high cell proliferative capacity is restricted to the embryonic life stage for humans and other mammals as there are no telomerase growth rates during the adult and senescent stages. Unlike in lobsters, most human somatic (body) tissues lack telomerase activity high enough to sufficiently regenerate telomeres. This is because humans, as other mammals, stop growing once they reach the adult stage. Following puberty, our size and weight are roughly constant measurements for the remainder of our lives. In contrast, lobsters do not stop growing once they reach the adult stage. Thus, high telomerase activity is observed in all lobster tissues due to their need to consistently shed their shells and adapt their exoskeletons accordingly (7).

Therefore, as it stands, telomerase is not a mechanism through which humans can achieve biological immortality for now. In 2018, however, the telomerase enzyme was modeled with the best structural detail to date, indicating an important step for research into development of drugs that could target specific regions on the enzyme and thus, either inactivate or activate telomerase (11). Meanwhile, a Stanford research team has also discovered a procedure for lengthening telomeres in cultured human muscle and skin cells by modifying messenger RNA, which carries DNA's instructions for protein and enzyme synthesis. Additional studies are being conducted to study the effects of this modified procedure in different cell types (12)

Hydra and FoxO Gene

Another organism of interest is the *Hydra* flatworm, a small jellyfish-like invertebrate that resides in freshwater environments. Under controlled laboratory conditions, it was discovered that the *Hydra,* remarkably, do not exhibit signs of aging nor seem to die of old age. Regardless of the age of the *Hydra,* all organisms in the study overall displayed extremely low, constant mortality rates. In addition, fertility in *Hydra* did not systematically decline with age. This is in contrast with biological aging processes, which involve increasing death rates and/or decreasing fertility with advancing age (13).

Hydra's biological immortality is facilitated by its asexual mode of reproduction, budding, in which a new individual develops from an outgrowth at a specific site on the parent organism. Formation of this outgrowth requires

cell division, which in turn, demands the *Hydra* to be able to consistently replace its old cells and produce a constant influx of new cells.

The *Hydra* is made up almost entirely of stem cells, which are the body's raw material or precursors; stem cells can divide to produce cells with specialized functions such as muscle cells or skin cells (14). All three of Hydra's stem cell lineages (ectoderm or outermost layer of cells, interstitial, and endoderm or innermost layer) strongly express the FoxO transcription factor, which activates a wide variety of target genes related to aging and cellular lifespan. Some of FoxO's functions include regulating apoptosis (programmed cell death), DNA damage repair, stress resistance, and cell cycle arrest (inhibiting a cell's progression through the cell cycle, which includes cell division) (15).

FoxO's high expression in all 3 of *Hydra's* stem cell lineages posited it as a viable candidate for promoting indefinite stem cell self-renewal and thus, biological immortality in *Hydra.* To further confirm FoxO's role in *Hydra*'s endless regeneration, gain-of-function coupled with loss-of-function studies were conducted. A gain-of-function study enhances a gene's expression to emphasize and better observe its effects. When gain-of-function of FoxO was induced, 2 main effects were observed. Firstly, FoxO overexpression (in the interstitial stem cell lineage) correlated with an increase in stem cell expression and proliferation. Significantly, the more stem cells an organism has, the more biologically immortal cells it has since stem cells can divide and renew their supply indefinitely. Furthermore, FoxO overexpression (in the interstitial stem cell lineage) also activated stem cell genes in terminally differentiated somatic cells, or cells that have irreversibly lost the ability to divide due to specializing in function (16).

In contrast, a loss-of-function study silences a gene's expression to observe the effects. When FoxO expression was silenced, 2 significant effects were identified. In juxtaposition with the results of FoxO overexpression, FoxO down-regulation correlated with a reduction in stem cell activity. This reduction in stem cell activity can plausibly be linked to the observed physical enlargement of the *Hydra* "stalk" or "foot" region, which signifies an increase in the number of terminally differentiated (foot) cells. In addition, reduced stem cell activity can also be plausibly linked to the drastically decreased population growth rate in silenced FoxO *Hydra* populations, which likely indicates slowed cell proliferation. Secondly, FoxO silencing also reduced expression of antimicrobial peptides, which function in *Hydra's* innate immune system. Overall, what is especially noteworthy is that FoxO silencing appeared to induce characteristics of aging in *Hydra*. Not only did signs of cellular senescence (lack of infinite cell division) appear, but FoxO - silenced organisms adhered to the immune-senescence theory of aging, which posits that the immune system declines with advancing age (17).

Altogether, it can be concluded that FoxO plays a key role in *Hydra's* biological immortality by promoting stem cell activity and maintaining innate immune defense. Is it possible, then, for humans to replicate *Hydra*'s infinite regenerative capabilities? FoxO goes hand-in-hand with biological immortality in *Hydra* because *Hydra* is made up almost entirely of stem cells that can divide indefinitely. Therefore, age-related cellular degradation cannot build up because old cells are constantly being replaced with new cells. On the other hand, FoxO cannot function in humans the same way it does in *Hydra* because most human cells are specialized, as necessary for the development of a large, multi-organ and complex organism. When cells specialize, they lose their ability to divide and create replacements for themselves when damaged (14).

Tardigrades and Cryptobiosis

Tardigrades, otherwise known as "water bears" or "moss piglets" are microscopic organisms found in a variety of permanent and temporary aquatic environments from the deep sea to the Antarctic. For a paper concerning longevity, tardigrades are noteworthy in that they are the most resilient species on Earth, possessing extraordinary capacities to survive hostile environments that few other species can. For example, tardigrades can survive up to 30 years without food or water, in temperatures as cold as absolute zero or as hot as above boiling, and at pressures that are 6 times the pressure of water in the Mariana Trench, the world's deepest ocean trench (19). In 2007, tardigrades became the first creatures to survive exposure to outer space, an environment, where in comparison, humans could only survive for

minutes unprotected (20). In addition, tardigrades were projected to be able to survive a variety of global cataclysms from large-scale asteroid impacts to supernova explosions (21).

Unlike the other organisms examined in this paper, tardigrades have naturally short lifespans, living approximately 2.5 years in the wild. However, tardigrades offer a different perspective on mechanisms for prolonging lifespan as paradoxically, these creatures can pause their biological clocks by several decades and live up to 30 years by entering the cryptobiotic state (18).

Cryptobiosis is a reversible standstill of metabolism, the group of chemical reactions that convert the energy in food into energy for basic body functions such as digestion or circulation (22). When their surrounding environment suddenly changes, tardigrades enter cryptobiosis, which provides them with an extraordinary tolerance to abnormal, hostile conditions including desiccation/dehydration (anhydrobiosis), rise in external osmotic pressure (osmobiosis), and freezing temperatures (cryobiosis) (18).

In cryptobiosis, tardigrades roll themselves up into a tiny indestructible ball known as the "tun state" by rearranging its internal organs, contracting its muscles, and retracting its 4 pairs of legs. Muscle protein filaments and cytoskeletal filaments stiffen to "lock in" or stabilize this new three-dimensional structure. In the process, tardigrades also reduce their body volume by 85-90% by retaining only 2-3% of its body water (18).

Releasing water is a key priority in cryptobiosis as water is considered a vector or vessel for environmental harm. For example, if exposed to freezing temperatures (cryobiosis), the water inside cells are likely to freeze. When this occurs, it is similar to if an icicle were to form inside a balloon. Just as the icicle can grow large enough to puncture the balloon, frozen water inside cells can pierce the cell membrane, damaging it enough so that it can no longer function. Without a working membrane, the cell cannot regulate the exchange of materials with its environment and thus, dies (23). In addition, the loss of water is necessary to halting metabolism, which requires water (24). According to the "rate of living" theory of aging, there is an inverse association between an organism's rate of metabolism and its lifespan, whereas stopping metabolism could lengthen lifespan by conserving energy (5).

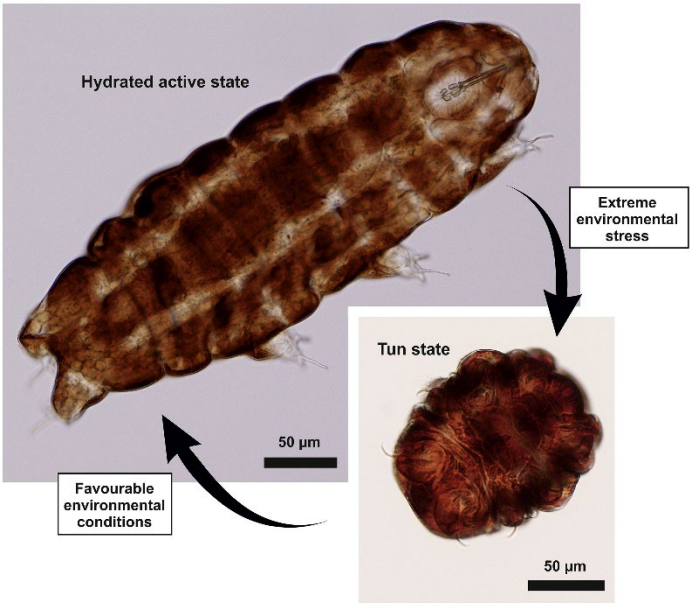

Figure 2 (18) Tardigrades cycle between cryptobiosis (halted metabolism) and active metabolism as they cycle between hostile and favorable environmental conditions, respectively.

For this paper concerning longevity, what is also fascinating is that cryptobiosis confers such an extraordinary capacity for surviving hostile environments that tardigrades are considered the most resilient species on Earth. For example, tardigrades can survive up to 30 years without food or water, in temperatures as cold as absolute zero or as

hot as above boiling, and at pressures that are 6 times the pressure of water in the Mariana Trench, the world's deepest ocean trench (19). In 2007, tardigrades became the first creatures to survive exposure to outer space, an environment, where in comparison, humans could only survive for minutes unprotected (20). In addition, tardigrades were projected to be able to survive a variety of global cataclysms from large-scale asteroid impacts to supernova explosions (21).

One of the enduring mysteries of organismal physiology regards how tardigrades are able to survive desiccation (anhydrobiosis) or dehydration. The trehalose sugar is a well-known bioprotectant essential to cryptobiosis in other anhydrobiotic organisms. For example, according to the water displacement hypothesis, trehalose replaces water during desiccation and stabilizes cell membranes so they do not rupture as they dry out (18). Along with cellular membranes, evidence suggests that trehalose can also protect proteins from inactivation (25). According to the vitrification theory, in freezing temperatures (cryobiosis), trehalose can also induce rapid-cooling or flash-freezing of intracellular liquid to form a glass-like substance in place of ice crystals, which could damage cell membranes (18). Additionally, trehalose forms viscous (thick) intracellular liquid environments that slow down the rate of damage accumulation within the cell (26).

Surprisingly, however, trehalose has been found at low levels or not at all in tardigrades, leading its role in tardigrade cryptobiosis to be debated. Pioneering studies suggest that trehalose may work in tandem with other bioprotectants to confer a synergistic benefit for anhydrobiotic tardigrades. 1 such bioprotectant are the intrinsically-disordered CAHS proteins (24). Intrinsically disordered proteins lack a fixed structure, while traditional proteins typically have a specific folding shape in relation to their specific functions. This variable structure makes intrinsically-disordered proteins (IDPs) responsive to changes in their environments. The CAHS protein is 1 example of a "tardigrade disordered protein." (TDP) TDPs function according to the vitrification hypothesis, forming a glass-like substance that slows down the rate of damage accumulation and protects other proteins from denaturation (destabilization of their structure) (27). Other studies suggest a synergy between trehalose and heat-shock proteins, such as Hsp-12, that stabilize protein structure when exposed to stressors such as increased temperatures (28). Still, other studies indicate the importance of the Dsup protein, a damage suppressor that binds to and protects DNA from hydroxyl radicals found in soil, water, and vegetation (29).

With all that said, is cryptobiosis a viable mechanism for such biological immortality in humans? The answer is a likely no. Trehalose, a bioprotectant that is crucial to cryptobiosis in many anhydrobiotic species, cannot be synthesized or stored by any vertebrate species. Instead, it is broken down into glucose (25). Moreover, both D-sup and tardigrade disordered proteins, as the name suggests, are tardigrade-specific substances (29).

Turritopsis Dohrnii Jellyfish and Transdifferentiation

The final and perhaps most exciting organism for current researchers is *Turritopsis Dohrnii,* the "immortal jellyfish," which possesses a revolutionary ability to seemingly turn back time and return to an earlier stage of its lifespan. Unlike other jellyfish, if an adult *Turritopsis dohrnii* experiences damage, environmental stress, sickness, or old age, it absorbs its own tentacles and reverses its development to its young, sexually immature polyp form. (Polyps are small, stalk-shaped animals with 1 end attached to a surface like coastal reefs or the sea floor) This is similar to if a butterfly reverted back to being a caterpillar and subsequently regrew into a butterfly (30). This mechanism is transdifferentiation or the reversion of differentiated/specialized cells to stem cells, which can differentiate again into a different cell type (31).

Through a theoretically indefinite capacity to revert back to an earlier stage of its lifespan, the "immortal jellyfish" defies death and avoids dying of old age. In the current state of research, it is little understood how transdifferentiation is possible. 1 insight was recently gleaned when *Turritopsis dorhnii*'s genome was mapped for the first time and compared to that of its relative, *Turritopsis rubra,* which ages normally. Noteworthy findings that warrant future investigative work include variants and expansions in genes associated with DNA replication and stem cell population. *Turritopsis dohrnii* had mutations that conserved telomere length and twice as many genes that regulate DNA repair and code for restorative proteins (32). With the "immortal jellyfish" genome mapped, a new line of study

has been opened. Additional research is necessary to further pinpoint the synergistic effect of the aforementioned molecular pathways in conferring biological immortality and to evaluate potential applications for human regenerative medicines.

Discussion

Much research is still needed to understand the mechanisms underlying senescence and to explore the possibilities of biological immortality in humans. Pioneering studies are constantly being published on new biological molecules, processes, and organisms that shed new light on the age-old mystery of aging. What will never get old, though, is the lesson of the classic cautionary tale, *Frankenstein.* The expansion of the wealth of knowledge on biological immortality demands diligence as unrestrained scientific research without regard for consequence can have disastrous results, as in *Frankenstein.*

One intriguing consequence of tampering with existing mechanisms for biological immortality concerns the relationship between telomerase and tumor suppression. Evidence points to telomeres as being "molecular sensors" that detect and limit replication of cells with damaged DNA. If telomere shortening is prevented in order to lengthen lifespan through endless DNA replication, cells can propagate copies of themselves regardless of how much DNA damage they have accumulated. Indeed, 90% of all malignant tumors (cancers) activate telomerase to prevent telomere shortening, enabling cancerous cells to divide indefinitely and invade other parts of the body. Therefore, repressing telomerase activity and maintaining short telomeres, despite it limiting cell division and thus human lifespan, is an important natural defense against cancer development (33).

Meanwhile, the *Hydra,* which is biologically immortal because it can continuously replace all its old cells, is not a desirable model for humans to mimic either. After all, we would not want to simply replace our neurons, which store our memories (14).

The transdifferentiation of the "immortal jellyfish" also carries potential for its own unique consequences. If cells were constantly starting over and switching functions, our immune system may be perpetually relearning how to fight the same diseases over and over again. Re-vaccinations throughout lifespan would become the new norm. A perplexing concept to also consider is the "Ship of Theseus" thought experiment, which questions if a ship that has had all of its original components replaced will still be the same ship after. Along that line of reasoning, it is unclear and heavily debatable if a human who has had all their cells replaced/restarted will still be the same human after.

Finally, it is crucial to remember that even if, theoretically, in a perfect world, biological immortality in humans is achieved, this does not mean that we would live forever. Rather, we would still die of extrinsic causes such as fatal accidents or environmental disasters (which would intensify if climate change worsens) (14). Unfortunately, this would likely mean that death would be more tragic as it would be more unexpected without a known limit on the human lifespan.

Conclusion

Biological immortality is the state in which mortality rates do not increase over an organism's lifespan. While death from extrinsic causes such as disease or predation is still possible, the organism will not die of old age. Scattered across the animal kingdom are the several rare instances of biological immortality, each made possible by distinctive and complex mechanisms. The lobster possesses an endless supply of the telomerase enzyme which preserves its telomeres and equips it with indefinite DNA replication and cellular division. The FoxO gene in *Hydra* flatworms contributes to high stem cell activity and quantity in addition to maintaining innate immunity. Tardigrades employ a synergy of trehalose sugar, tardigrade-disordered proteins, heat shock proteins, and damage suppressors to temporarily halt metabolism in cryptobiosis. Cryptobiosis pauses tardigrades' biological clocks and allows them to endure hostile environments that few other species can. Meanwhile, the *Turritopsis dohrnii* jellyfish cheats death through

transdifferentiation, a process of reverting back to an earlier stage of its lifespan by de-specializing and re-specializing its cells.

As of right now, it is not possible for humans to achieve biological immortality by mimicking the aforementioned organisms. Our anatomies and physiologies are not only different, but we lack key molecules either altogether or in the necessary quantities. However, these organisms can inspire further research that can aid humans in living healthier lives such as by improving the function of our cells as they age. In general, though, additional research is needed to cement understanding of the mechanisms behind aging as no theory of aging is currently universally agreed upon. Even so, humans may never achieve biological immortality, but that may be the best course as the aging process is embedded within a delicate network of integral biological functions not limited to DNA preservation and replication, metabolism, immunity, and stress response. Tinkering with any part of this network could have untold consequences in another. Perhaps, instead, as the all-knowing Ancient One in the iconic superhero film, *Doctor Strange,* articulates, there is beauty in knowing our days are numbered.

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