TERM PAPER ON BIOTECHNOLOGY OF AGING

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1. Introduction:

What a pleasant experience just to think about not being old. Does bioscience stop aging? This is one of the important questions among bioscientists. A lot of research has been conducted towards answering this question, "Does bio-science stops aging?" This paper will review the relationship between aging and biotechnology as well as the current biotechnology applications and discussion on its ethical part and future development.

Multiple aging theories have been developed in this 21st century, yet the mystery of aging remains unsolved. Lifetime, life conditions, and aging are determined by multiple factors. Aging is an interrelated mechanism acting at different biologic levels (Brooks-Wilson AR., et al., 2013). Age-related transformations are related to changes in the cell number, tissue composition, impairment of cell-to-cell signaling, and inability or compromise to respond to stress and metabolic changes (Brooks-Wilson AR., et al., 2013).

Epigenetic changes, telomere attraction, and alteration in gene expression and metabolic concentrations are aging biomarkers. More than dozens of aging clocks are available and most of them use molecular features to predict age. Identifying biomarkers of aging is one of the ways to define biological age (BA). Multiple features and traits transform at different levels of the age of any organism which will be known as biomarkers of aging. While aging is being studied based on its biomarkers, some group of scientists says that age has no distinct genetic connection. Age has heavily relied on socioeconomic and cultural differences. On the other hand, aging also depends on its definition, of what stage of the body is considered aging.

National Center of Health Statistics 2005 stated that, by 2030, the number of people in the United States aged 65 and older is expected to double. Diet, exercise, lifestyle, the invention of technologies in healthcare, and many more have played important roles in this increasing life expectancy. This review will deep dive into the technical aspect of it focusing on biotechnology. The scientific revolution in molecular biology has made tremendous positive effects on the aging population. Recent development in the human genome opens intriguing possibilities such as the development of drugs based on the individual's genetic makeup, which makes it possible to replace defective genes or gene products (Read, Catherine Y., et al., 2008).

Health spanners believe that one-day science will delay the onset of aging-related conditions (Read, Catherine Y., et al., 2008). Recent advancement in biotechnology has led to a better understanding of the human genome and has opened doors to exciting new possibilities for improving the quality and duration of life (Ocampo, Alejandro, et al., 2016). The idea of replacing unhealthy tissues and organs with healthy ones made with steam cells is gaining widespread acceptance around the world.

2. Application of Biotechnology:

Stress is one of the contributing factors to aging. Biologically being able to increase resistance level to stress will delay the aging process. Simply by using this theory, biotechnologists have been able to do a lot of studies and inventions which show high potential to delay aging. The age of any species is seen directly related to its stress-resistant power. Studies showed that Arctica islandica, the longest-living non-colonial animal is more resistant to oxidative stress at the

cellular level compared with shorter-lived Mercenaria (Ungvari Z, et al., 2011). Scientists can trigger longevity by inducing mutations in the gene that suppress it under favorable conditions. Activating stress response genes encoding transcription factor FOXO NRF2, HIF-1, and JNK kinase, sirtuins are also one way of reducing stress and increasing longevity (Brooks-Wilson AR., et al.2013). The other way is the NRF2 signaling pathway which is increased/activated when an individual receives medications for the treatment and prevention of cardiovascular, kidney, lung, or liver disease. The same principle applies to the treatment of metabolic or autoimmune disorders, chronic inflammation, epilepsy, or malignant tumor prevention (Pall ML, Levine S., 2015). The transcription factor Nrf2 is considered a master regulator of detoxification and antioxidant in the development of health promotion factors. Many medications and health-promoting factors have been developed based on this principle of gene encoding transcriptions and stress resistance.

Another contributing factor to aging is cell malfunction. The inability of cells to repair damaged macromolecules causes diseases like cancer and tumors. The application of telomeres knowledge to control and treat cancer is particularly found interesting. Telomers are stretches of DNA that protect the ends of chromosomes and the addition of telomerase enzyme to healthy cells could keep them from aging (Dunshea, Glenn, et al., 2011). Telomerase Reverse Transcriptase (TERT) is a catalytic subunit of the enzyme telomerase and it is regulated by a variety of mechanisms. Cancer cells have significantly shorter telomeres. Most malignancies lead to reactive TERT expression, which in turn activates telomerase to allow for continued proliferation. These molecular markers have begun to be used in making clinical decisions in thyroid cancer. The TERT mutation is a predictive marker of distant metastases. However, the TERT mutation status is not used for initial risk stratification (McKelvey BA, et al., 2020).

Lifespan directly relates to the efficacy of DNA repair. Understanding telomerase complexes help to understand various types of cancers. In human cancers, telomerase is reactivated by the expression of telomerase reverse transcriptase (TERT). Single nucleotide polymorphisms (SNPs) may be in intronic and exonic sequences of TERT and are found to be associated with an increased risk of developing various cancers. Several studies were conducted to identify new SNP loci related to telomere length which can also give information about disease severity, survival time as well as the risk of disease (Dratwa M, et al., 2020). A cohort study conducted by Ricardo in 2009 suggests new findings on Urothelial Bladder Cancer (UBC). In UBC TERT activation can occur in the presence or absence of mutation. Hypermethylation of the TERT promoter plays a key part in such cancer, being a dynamic and progressive process, with hypermethylation level increasing with bladder cancer severity. These findings found in UBC may be applicable to other tumors (Leão R, Lee D, Figueredo A, et al., 2019). Furthermore, there are more factors contributing to analyzing telomere length correctly in blood analysis. Less lymphocyte count will make telomeres of different lengths. Results may be biased from the truth if the blood component is not accounted for during the study (Galkin F, et. al., 2020).

Growth hormone (GH) and insulin-like growth factor (IGF-1) play an important role in aging. Many studies have been done to understand how these mechanisms work in living beings. A study is done to understand how tyrosine kinase activity works and how this pathway can be triggered to enhance cell metabolism and growth. Experiment shows that the disruption of these IGF-1 extends the lifespans of yeast, nematodes, insects, and mice. Similar observations were made in studies of the suppression of the GH/IGF-1 axis in the human population (Moskalev AA,

et. al., 2017). Similarly, the signaling pathway of the transforming growth factor beta (TGFB) is involved in a lot of cellular processes. Similarly, factor TGFB supports the induction of gene markers of cellular aging and participates in the formation of the senescent cell phenotype under oxidative stress (Baye, Tesfaye M., et al., 2011). Polymorphism in the coding sequence of TGFB in humans is associated with longevity (Frippiat, C., et. al., 2002).

Another mechanism of increasing age is proteostasis. Proteostasis is the set of mechanisms controlling the quality of cellular proteins. Proteostasis disbalances the biomarkers of aging, which adversely affects lifespan (Chondrogianni N, et. al., 2012). Proteins in the cell are affected by various internal and external factors. Damaged proteins influence several intracellular pathways resulting in various disorders and diseases. Aggregation of those damaged proteins depends on the balance between their generation and their reversal or elimination by the protein repair and degradation system in the body. Genetic modulation is being studied based on the fundamental principle of protein repair and degradation. Different drugs as well as natural compounds that interfere with proteolysis have been identified so far which maintain a homeostatic environment and delay disease progression.

Chronic inflammation in tissue is one of the causes of aging. At the cell level, the inflammatory response is triggered by signaling pathways related to the activity of transcription factor BF-kB. The activity of NF-kB increases with age and results in age-related chronic disorders. Suppression of inflammatory process is among the efficient ways to prolong life. Ibuprofen and acetylsalicylic acid in nematodes were found to be useful for life extension (Ayyadevara S, et. al., 2011).

Understanding adipose signaling pathways will help to understand many associated diseases such as insulin resistance, hyperglycemia, dyslipidemia, hypertension, and metabolic syndrome. Myostatin is another age-related cytokine that belongs to muscle tissue growth. The muscle mass of humans directly co-relates with lifespan.

Furthermore, in vitro studies have demonstrated that cellular reprogramming to pluripotency reverses cellular age but alteration of the aging process through reprogramming has not been directly demonstrated in vivo (Ocampo, Alejandro, et al., 2016). Genomic study in biotechnology has made it possible to develop medicine based on individual genotypes or genetic makeup which is likely to revolutionize the concept of modern medicine (Shi, Michael M., 2002).

3. Discussion

Genomic study and biotechnology are rapidly growing fields of research. Genomic sequencing has undergone massive expansion in the past decade. The transition from one-gene sequencing to whole-exome sequencing was made possible due to advancements in technologies and informatics. This technological advancement has made tremendous effects in many fields including aging. Defining age and determining biological age is basic for an increased lifespan so many biological tools and technologies focused on defining age and looking for a possibility of increasing lifespan. Various available aging clocks indicate a great need for further investigation to determine the exact or nearest biological age. Quantifying and measuring biological age and measuring its progression is still controversial despite having multiple aging-

related theories. Despite having that conclusive idea of no biological age, the benefits of developed age-related therapies are likely to be biased.

Various studies justify the correlation between longer telomeres and increased lifespan both in organisms and human beings. But these studies have also failed to give consistent results due to multiple reasons such as telomer measuring method, different sample sizes, and age distribution. So far telomere aging clock remains a hypothetical concept (Carrieri G, et. al., 2004). Despite of affordable price of clinical biochemistry data is not assessed for a long time for its potential for aging biomarkers. The first aging clock based on blood biochemistry was introduced in 2016 (Carrieri G, et. al., 2004). Despite having a lot of information on telomerase regulation, information is not being used to make clinical decisions.

There is an ethical dilemma in the use of biotechnologies. Are these technologies supposed to be used to declare aging, freedom from chronic disease, or prolonged life? Many scientists are against prolonging life merely for life's sake. It should be regarded as therapy and freedom from chronic diseases (Read, Catherine Y., et al., 2008).

Regulation of antiaging technologies is another topic of discussion. Strict regulation is required in this field, especially on antiaging technologies to protect consumer safety, prevent adverse economic consequences and ensure equitable access to technologies.

Genotypic environmental interaction is complicated by multiple factors including phenocopies, genocopies, and others. A better understanding of GEI is essential if patients are to make informed health choices guided by genomic information (Baye, Tesfaye M., et al., 2011). Thus, extensive study is required to reach the level of health choice decisions based on genotypic information.

There is a major gap in biotechnology knowledge when it comes to aging and its use in clinical decisions. Most of the studies are fractional and not institutionalized so knowledge gained so far in biotechnology is not being used properly and completely in making clinical decisions. On the other hand, further studies are needed to make clinical decisions with enough research evidence. For example, further studies are needed to determine the true utility of the TERT mutation status in the clinical setting and how to best target TERT regulation (McKelvey BA, et.al., 2020).

Many religious leaders argue that the project of lengthening lifespan is truly ambiguous. The use of anti-aging technologies may foster a hostile nature towards the human body and its limitedness. We may be living in a "mass geriatric society" where a growing percentage of the US population is expected to be 85 years and more (Daly TTW., 2022). This situation is foreseen as a significant increase in age-related maladies such as Parkinson's high blood pressure, dementia, and heart disease. This change in demographic will continuously increase the burden on US health care. Alzheimer's and dementia cost over 200 billion USD in 2020 only for Medicare and Medicaid which is a more expensive treatment than cancer and heart disease (Alzheimer's Association 2020). The estimated cost of Alzheimer's treatment in 2050 will be 584 billion USD due to the increase in disease (Alzheimer's Association 2020). Longevity Dividend Initiative Consortium (LDIC) demands more resource allocation for studying human aging itself (Daly TTW., 2022).

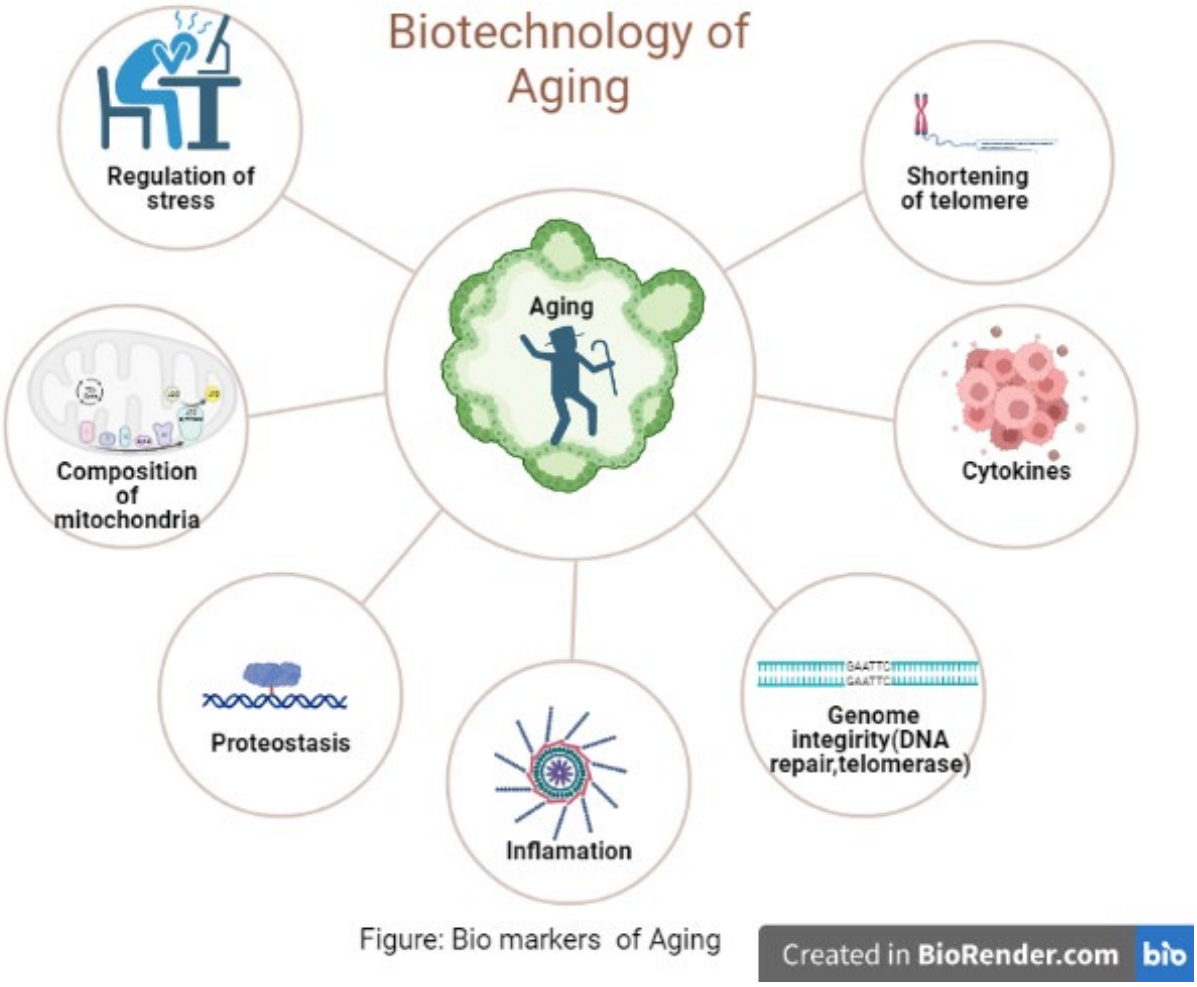

Figure: Bio markers of Aging

(Source: Aging and its determining factors as per A.A Moskalev. "Genetics of Aging and Longevity")

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