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Can gene expression delay aging and increase longevity?

Abstract

The reality of interacting genes and proteins is vastly complex and intricate with many unknowns which currently prevent us from solving the anti-ageing equation in terms of gene expression. Molecular studies involving genome modification should take into consideration the importance of apparently opposing genes and proteins which when seen as a whole, can orchestrate an optimal systemic balance. Gene expression is often a double-edged sword with positive effects turning negative when a particular gene is overexpressed. For this reason, the US National Academy of Sciences and the National Academy of Medicine have placed stringent restrictions on the promising genome editing methods to be used only for the specific DNA sequence associated with a transmissible genetic disease. Rejuvenation as a result of gene expression is still an open area of research with studies that have either been limited to in vitro research or clinical studies claiming success based on a limited perspective that selectively emphasises the benefits of certain genes while leaving the negative outcomes in the shadows of their silence. For example, some investigators relate the presence of ZMPSTE24, IGF1R, NGF4, EEF2, EIF4FBP1 CCL18, and other genes with "rejuvenation," selectively focusing on potential benefits while ignoring the involvement of some of these genes in malignancies and inflammation. Well-controlled gene expression molecular experimental studies with mechanotherapy and effortless exercise have limited themselves to the observation of increased slow skeletal genes associated with muscle growth that do not present any adverse side effects. Overall, exercise and nutrition are still the safest and most ethical methods of gene expression at least until genome editing can be extended to delaying ageing, in the near or distant future. As observed in the research analysing gene expression as the result of different types of exercise, inflammatory events are counterbalanced by antagonizing anti-inflammatory ones. This signifies optimal biological homeostasis because health depends on the harmonious interaction of opposite processes levelling and stabilizing each other. Exercise modalities and lifestyle are still representing the cornerstone of delaying ageing and the most riskless method of increasing longevity by triggering processes that balance each other.

Keywords: longevity, RNA, DNA, anti-ageing, proteins

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Introduction

Can gene expression delay aging and increase longevity?

Scientific endeavours in the past century have been largely dedicated to enhancing longevity. From the 1900s to today, life expectancy has increased from an average of 47.3 to 78.7 years old[1]– a statistic that could signify a major accomplishment. From 1950 to 2010 length of life has increased by around 10 years from 77 to 87 years of age. It should be noted, however, that this phenomenologically high percentage reflects a minimal absolute increase of one year for men and two years for women at the age of 85, and only half of that at 95.[2] Regenerative and Anti-aging medicine has focused on developing technologies that maintain the necessary health indices involved in longevity. They have emphasized the importance of rudimentary proteins like collagen and elastin which are currently the stars of popular rejuvenation methods.

Telomeres and telomerase

Other investigative bodies have focused on shortening of telomeres, the protective molecular caps at the ends of chromosomes that undergo attrition every time a cell divides. Shorter telomeres lead to cellular senescence and apoptosis which become inevitable during the aging process. Shortening of telomeres has been highly correlated with adiposity, insulin resistance and Type 2 Diabetes patients who manifest shortened telomeres when compared to normal controls. Telomere length is positively associated with increased high-density lipoprotein (HDL), optimal glycaemic control and overall content of the mitochondrial DNA (mtDNA) that converts the fat contents into different forms of energy like Adenosine Triphosphate ((ATP) that are essential for the sustenance of an organism.[3] Lifestyle, proper nutrition and physical activity can delay telomere attrition and enhance longevity.[4] Driven by the simple deduction that longer telomeres will offer the fountain of youth, several researchers have. Recent studies examined people ages 7-83, with mutations in the POT1 gene which plays a role in telomere length regulation. Results did not support the hypothesis that longer telomeres will delay ageing. On the contrary, they outlined the dangers of longer telomeres: Fifteen out of the 17 subjects evidenced both malignant and benign neoplasms. Five had blood-related cancers, eight had skin melanoma and seven had thyroid cancers.[4–6]

Longevity genes

Longevity genes have been indeed identified such as the APOD, FOXO3 and CETP genes which, however, are not found in all individuals whose genetic predispositions have allowed them to live longer. Pro-longevity genes have been studied in primary organisms using predictive algorithms that calculate the possibility that a particular gene will have on lifespan. A list of genes has been unveiled that includes CLED-196, F44E5.4, CEH-13, LPR-3, HIL-7, W04A8.4, GST-1, FAAE5.5 and F20C5.6.[7–18]

Longevity and epitranscriptomics

Epitranscriptomics signifies deep sequencing identification and mapping of RNA fragments. This method provides a wealth of information about underlying biological processes, including revelations in viral research performed on COVID-19 which involves specific RNA modifications such as N6-methyladenosine (m6A).[19,20] The ageing epitranscriptome involves over 150 specific editing events that affect RNA regulations and different aspects of tissue regeneration. RNA modification can be beneficial in extending life or may signify dysfunctional processes resulting in neurodegenerative, cardiovascular, and autoimmune diseases.[21]

DNA methylation and chromatin organization

There are several other interventions such as DNA methylation that typically acts to repress gene transcription, histone modification and nuclear organization that affect the 3-D chromatin organization, chromatic remodelling, which is the rearrangement of chromatin from a condensed state to a transcriptionally accessible state so that other proteins bind with the DNA and participate in gene expression. Additionally, there is the method of non-coding RNAs that claims to delay the epigenetic changes that are evidenced during ageing.[22] Chromatin is a mixture of DNA and histones that act as librarians packaging the books back onto their selves according to their categories. Histone modification is also involved in the formation of the sequential structure of chromatin as shown for example, by genes that are expressed as a result of H3K9ac being acetylated and silenced when H3K9ac is methylated.[23] But most of this research has been conducted in vitro, providing knowledge based on molecular biology experimentation without offering actual clinical interventions that can, in fact, utilize gene expression to delay ageing or extend life per se.

Genome editing

Genetic manipulation has been the target of several laboratories aiming to rewire mutated genes and restore them back to normal as a therapeutic intervention in the treatment of genetic disorders. They have developed different versions of genome editing that include a variety of enzymes like "meganucleses" (MNs), "zinc finger nucleases" (ZFNs), "clustered regularly interspaced short palindromic repeats" (CRISPR) which are transcribed by CRISPR associated Cas proteins (CRISPR-CAS) into short interfering RNAs (crRNAs) forming part of the ribonucleoprotein complex, and "transcription activator-like effector nuclease" (TALENs). Small interfering RNA (siRNA), short hairpin RNA (shRNA) and bi-functional shRNA molecules are also administered to promote the expression of specific genes. This is a promising method. However, exogenous proteins like ZFNs, TALENs and CRISPR-Cas can trigger an adverse immune response in some patients. Additionally, there is the risk of producing an abnormal rearrangement of chromosomes also known as unbalanced chromosomal translocation.[24–26] Surely, genome editing may be a very attractive therapeutic route for patients with genetic disorders.

Ethical considerations

A number of ethical concerns have been raised regarding genetic editing primarily focusing on technologies using the clustered regularly interspaced palindromic repeats (CRISPR)/Cas9 method. The committee of the US National Academy of Sciences and the National Academy of Medicine have restricted genome editing to the following conditions:[27]

I. Only when genome editing is utilized to prevent the transmission of disease.

II. Only when it exclusively modifies the specific DNA sequence that is associated with the genetic disease.

III. And only when the "genetic modification is conducted under a stringent set of ethical and regulatory requirements".

According to these regulations, genome editing procedures should be considered illegal or unethical for all individuals who pursue facial rejuvenation and life extension. The reason for these stringent restrictions is the fact that gene expression is a complex process with covert, undiscovered aspects and missing information, like an unsolvable mathematical equation with too many unknowns. Several genes may control the expression of one gene. Genes code proteins which in turn control the expression of other genes. So a number of proteins say "A, B, C …n" controls the expression of "gene I" which is transcribed to mRNA. Gene's "I" mRNA is translated into protein "Ii" which is in turn controlled by "D, E, F,…n" proteins. In other words genes are part of an intricate interactive network that may differ depending on molecular collaborations and interfaces. Additionally, most genes have both positive and negative effects depending on the timing of a gene's appearance within the context of the sequence of proteins and genes that control them.[28]

Epigenetic reprogramming

Epigenetic reprogramming combines a specific genotype with environmental influences to compose a phenotype, forming a new composite that consists of intricate unique transformations that define and explain individual differences in entities with identical genetic information. This process combines histone modification, DHA methylations and non-coding DNAs with developmental epigenetics which prepare the organism to cope with environmental challenges. Obviously, this interaction is significantly affected by lifestyle, the environment of a particular, geographic location, chemicals and other pollutants.[29]

Upregulating antioxidant genes

Another line of research is pursuing the upregulating of antioxidant genes by manipulating hormonal levels and nutrition. Some of this research is based on the observation of the female advantage in longevity over males in a wide range of different species. It has been noted that female mitochondria produce 50% less H_20_2 than males. Additionally, females overexpress glutathione peroxidase and superoxide dismutase as a result of oestrogens stimulating the mitogen-activated protein (MAP) that transmits signals from a receptor on the cell surface to the nuclear DNA. Oestrogens also activate the nuclear factor kappa B (NF—kB) signalling pathway that serves as a regulator of innate immunity.[30]

Gene expression via intense pulsed light

Research by broadband light has focused on a rather limited examination of gene expression, isolating specific genes and emphasizing the aspects that fit their rejuvenation hypotheses, while neglecting the potential harmful effects that overexpression of these same genes may present.[31–32] The researchers are affiliated with Stanford University, however, research cited was financed by Sciton, a company producing medical and aesthetic laser technologies, the Nu Skin multilevel marketing company and others. Initially, these investigators did not actually test facial skin but took biopsies from the forearms of healthy older females with moderate to severe photodamage on their forearms. They report that "the periodic

acid–Schiff stain showed no obvious changes in collagen quantity in the dermis between treated and untreated aged samples...” They claim that “elastotic fibres” were diminished, most likely trying to allege that elastosis, a process known as photoaging was diminished. However, they fail to mention if there were any new elastin fibres that would signify an improvement in skin elasticity. Importantly, these investigators were invested in verifying their hypotheses instead of falsifying them – a necessary requirement in all experimental science that must comply with validity and reliability principles. They postulate that they found “regeneration” genes as a result of the BBL treatment and cite only the assumed rejuvenation functions of several genes, despite the fact that all of these genes have dual functions that include inflammatory processes that actually speed up ageing as well as potential progression into malignancies.

Some of the “regeneration” genes mentioned by the BBL research are the following:

ZMPSTE24 (zink metallopeptidase STE 24)

This is a protease that cleaves proteins, involved in the processing of Lamin A, which plays an important role in nuclear structure and function. Mutation in the Lamin A is associated with Progeria (Hutchinson-Gilford syndrome) which represents the most severe syndrome of early aging.[33,34] However, recent research has reported that ZMPSTE24 overexpression is positively correlated with C-Reactive protein that signifies inflammation. Inflammation provokes overexpression of both ZMPSTE24 and lamin A/C RNA which are positively correlated with the premature ageing marker progerin.[35] In conclusion, a certain level of expression of the ZMPSTE24 gene may be related to anti-ageing. Yet, overexpression of ZMPST24 is associated with inflammation which speeds up the ageing process. Therefore, claiming that BBL produces an absolute “rejuvenation” effect appears to be an oversimplistic narrow perspective of the biological process underlying this trauma-based procedure that cannot convincingly exclude the possibility of inflammation. If BBL increases inflammation, then the inflammation-driven overexpression of ZMPSTE24 may in fact promote aging which is the opposite of rejuvenation.

IGF1R (insulin growth factor 1 receptor) is involved in cell growth, which would be an unfaltering aid for rejuvenation. Unfortunately, IGF1R is also associated with the development of malignancies.[36] Therefore BBL could be fatally deleterious in individuals with undiagnosed neoplastic processes developing insidiously.

NGF4 (nerve growth factor loop 4)[37] is essential in the development of both the peripheral and central nervous systems. It is associated with cognitive function and memory integrity, but it is not exactly a “rejuvenation” gene from an aesthetic or photoaging point of view. Nerve growth factor is defensively increased in inflamed tissues.[38] Therefore, the presence of NGF4 could simply demonstrate the presence of inflammation, which could provoke overexpression of the ZMPSTE24 gene promoting ageing,

EEF2 (eukaryotic elongation factor 2). Apparently, the BBL group implies that EEF2 will produce cellular regeneration and therefore delay ageing. In fact, EEF2 is associated with the tumorigenesis of gastrointestinal cancers and overexpressed in 92% of gastric and 91.7% of colorectal cancers. Research has confirmed that overexpression of EEF2 can promote the progression and enhancement of cancer cell growth in vitro and in vivo[39] -- a dangerous possibility that vulnerable patients cannot afford. Such facts should be clearly noted by the BBL researchers who only cite the benefits of EEF2 but not its risks, undermining the validity and reliability of their research.

EIF-4G1 9 eucaryotic translation initiation factor 4 gamma 1

This is a gene associated with Parkinson’s disease. “functional studies have suggested that these variants may impair the ability of cells to rapidly and dynamically respond to stress”.[40] Therefore, it is unclear why this gene is reported as a “rejuvenation gene” in the first place.

EIF4FBP1 (eucariotic translation initiation factor 4e binding protein 1) encodes the EI4FBP1 protein, also known as 4E-BP1 that is related to cancer and the worsening of malignancies. Again, it is unclear why this is featured as a “rejuvenation gene”.

MOV10 is involved in multiple RNA helicase activities and other gene expressions and may be an ancient form of immunity, but it has also been implicated in hypertension and hepatitis.[41]

CCL18 (motif chemokine ligand 18) is induced by helper 2 type cytokines, namely IL-4 and IL-13, both of which are associated with inflammation. CCL18 has also been implicated in enhancing hepatocellular carcinoma cell migration.[42,43]

HAS2-AS1 (hyaluronan synthase2-antisense 1) Hyaluronan is associated with hydration elasticity and cell survival. However, overexpression of the HAS2-AS1 gene causes cell dedifferentiation, which when coupled with cellular proliferation and migration can promote cancer, fibrosis and vascular wall thickening.[44,45]

There are many other genes cited by this BBL research but the scope of this paper is not to offer a complete review of their articles. The main point here is that gene expression is a complex process that can be more accurately described as a double-edged sword. This is the reality behind the glamorous façade promising eternal youthfulness. There are other lines of research that fulfil the scientific requirements of a null hypothesis, fulfilling the principles for validity and reliability. These studies examine the data from all perspectives both positive and negative rather than the selective limited perspective that can please a benefactor.

Genetic research on muscle hypertrophy

Goldpink’s article[46] on how “stretch and force generation induces rapid hypertrophy and myosin isoform gene switching in adult skeletal muscle” studied the effect of stretch and mechano-stimulation on “fast and slow myosin heavy chains and other genes.” According to these investigators stretch produced more proteins, increasing the tibialis anterior muscle by 30% within four days. The rapid hypertrophy was associated “with an increase of up to 250% in the RNA content of the muscles. Both stretch and mechanoelectrical stimulation alone “caused repression of the fast-type genes and activation of the skeletal slow genes.” A follow-up study by the same investigators[45] reproduced physical activity via mechanical stimulation to research the link between muscle cells and gene expression, since myosin heavy chain genes encode different molecular motors. In this experiment, they analysed the cloned cDNA of an IGF splice variant produced by the active muscle. The sequence analysis of the IGF gene showed a process of its binding to other proteins in the muscle, neurons and bone. They called this new growth factor mechano-growth factor (MGF) which is different from the liver circulating IGF-1 and specific to the skeletal muscle production of IGF-1 during regular exercise. IGF-1 induces hypertrophy through the calcineurin/calmodulin pathway. Interestingly, MGF is only found in normal muscle and not in muscular dystrophies and is assumed to be the link between the mechanical stimulus and gene expression. This study was replicated with similar and extended findings.[49–52]

Sofra et al[53–64] adopted a London University invention, completed in 2008 by G. Pollock, an electronics engineer, on the basis of his combined research with D. Gilbert, a molecular biology London University professor after 30 years of empirical research. The technology features a proprietary formula that synthesizes and regulates the complex waveforms which generate the sensation of a multi-exercise regimen, experienced as fast-paced or slow/resistance physical training. This 16-channel technology is hand-made, analogue to offer a series of voltage-driven, unlimited resolution waveform composites that produce 1000 full body musculature contractions per hour, each sustained for 8-10 seconds, with 2-secs rest time. An examination of all her studies found a combined average adipose tissue decrease of 47.81% that was statistically significant on all samples examined. She also found an overall muscle mass increase of 49.5% which was also statistically significant across all samples provided. Sofra also reported statistically significant changes in several other health variables that included optimal levels of C-reactive protein that decreased by an average of -36.87% as well as cortisol levels that decreased by -17.47% to be within the normal range. HDL showed an average normalized increase of 22.84% and Triglycerides a 40.84% decrease, while the visceral adipose tissue indicated a significant decrease of 33.41%. Free T3 was increased by 27% and testosterone increased by 50.04%. All these values were statistically significant and within the normal range. Sofra reported that this effortless exercise method improved liver health as determined by the sonography reports of patients with non-alcoholic fatty liver disease; this result was accompanied by an optimal decrease of creatinine by -19.67% and bilirubin by -12.33% -- both of which were previously abnormally high. ALT (alanine aminotransferase), AST (aspartate aminotransferase) and ALP (alkaline phosphatase) were optimally decreased by -24.83%, -30.407%. and -14.529% respectively. One of the most important contributions of this line of research is to emphasize the reduction of inflammation. Inflammation can disorganise hormonal balance and accelerate ageing which is usually accompanied by health deterioration and the development of several ageing-associated diseases.[65]

Ageing and inflammation

Inflammation should be the primary concern in developing anti-ageing treatments. Inflammations is the common denominator of a number of deleterious biological events such as DNA damage that leads to cellular senescence, dysfunction and death. Some investigators postulate the reinforcement of inflammatory processes that include cGAS-STING (cytosolic DNA sensing pathway) axis, one of the crucial guarding mechanisms that can avoid pathogen invasion and unleash a stress cascade orchestrating a protective immune response. They also mention the VF-kB signalling pathway or "*Nuclear factor kappa-light-chain-enhancer of activated B cells*" that regulates cellular growth and apoptosis.[66] Such research indicates that inflammation is pertinent to provoke an immune response that adversely affects the organism when it aimlessly continues past the point of its advantageous functionality. The more inflammation persists the more ageing is accelerated.

Overview

Although in vitro research on cellular reprogramming offers a beacon of light in clinical rejuvenation, most if not all studies have not been tested in clinical settings.[67,68] People are longing to find a technology that delays ageing, which is why facial rejuvenation studies like the one conducted by the BBL scientists have received such a warm welcome: Because they establish hope and fulfil wishful thinking by their claimed success on "rejuvenation," which is, in fact, based on a selective examination of genetic data, without revealing the possibility that the gene expression they are claiming to have discovered involves genes that can accelerate ageing when they are overexpressed, like their "star rejuvenation gene", ZMPSTE24, for example. This overview brings us back to what has been recommended by physicians for years such as nutrition, and different exercise modalities which have recently included effortless exercise to their repertoire that apparently produces long-term health benefits.[69–71] Some methodologies using signalling and ultra-low energies have documented wound healing and pain reduction.[72,73] Despite the statistically significant therapeutic results, no gene expression analysis was conducted to reveal the underlying mechanisms of skin repair and neuropathic pain relief.

Dietary restriction is one of the most effective nutritional methods. This includes intermittent fasting which has been proven to extend the life of mammals by upregulating the expression of the silencing complex of microRNAs (miRNSs). miRNAs normally regulate gene expression post-transcriptionally, controlling cell growth, division and differentiation as well as the metabolism and development of an organism. These miRNAs include argonaute proteins, key players in RNA silencing, and the GW182, which are also involved in miRNA gene silencing.[74] It should be noted that this type of research was conducted with Caenorhabditis elegans, a type of worm.

Clinical research has documented gene expression of over 311 genes as a result of exercise. As expected, exercise triggered the expression of stress and inflammation-related genes, like the shock protein 70, the dual-specificity phosphatase-1, and chemokine genes such as macrophage inflammatory protein-1alpha and 1beta. However, all these genes were downregulated during the rest period following physical activity. Normal T cells were also increased during exercise, indicating an immune enhancement. Interleukin-1, an anti-inflammatory agent, was increased as soon as exercise was terminated. Importantly, exercise upregulated growth and repair genes such as epiregulin, platelet-derived growth factor and hypoxia-inducible factor-1. Exercise also upregulated the PBMC gene expression which can be simultaneously beneficial by deactivating stress-associated genes and deleterious by activating stress-associated genes.[75–77] This phenomenologically contradictory manifestation of proteins and their associated genes is interpreted as homeostasis where opposing forces expressed in moderation provide systemic harmony. Exercise is health enhancing because it balances the body by providing it with both the defensive inflammatory/stress processes and the anti-inflammatory anti-stress processes that are necessary to extend life.

Conclusion

All biological processes are useful as long as they do not aimlessly continue past the point of their optimal functionality. Our tendency to classify molecular events into good and bad because it is easier to understand them by locking them into a specific distinct category is, in fact, incorrect and misleading. The reality of interacting genes and proteins is vastly more complex and intricate than we would like to imagine, and there are too many unknowns involved which currently prevent us from solving the anti-ageing equation in terms of gene expression. Molecular studies involving genome modification should take into consideration the importance of apparently opposing genes and proteins which when seen as a whole, can orchestrate an optimal systemic balance. As observed in the research analysing gene expression as the result of exercise, inflammatory events are counterbalanced by antagonizing anti-inflammatory ones, because

health depends on the optimal interaction of both of these opposite processes levelling and stabilizing each other. Optimum is not the absence of inflammation but the absence of inflammatory processes progressing beyond the point of their necessity. Exercise and any related methodologies are still representing the cornerstone of delaying ageing and increasing longevity by triggering processes that balance each other. Rejuvenation as a result of gene expression is still an open area of research with studies that have either been limited to in vitro research or clinical studies claiming success based on a limited perspective that selectively emphasises the benefits of certain genes while leaving the negative outcomes in the shadows of their silence.

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Conflict of interest

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