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Why do we age? questions and answers in regenerative medicine

Abstract

Aging is a multidetermined collective process reflecting desynchronization of molecular interactions with persistent disintegration of Proteostasis. Hormonal imbalance, DNA damage, elevated toxicity and inflammation are central to the body's eventual disharmony as time goes by. Impairment of autophagy and mitochondrial function, reduced stem cells' differentiation, and interruption of cellular trafficking or distortion of exosome signals accumulate to disentangle cellular communications, inevitably triggering physical dysfunction. Most aging theories are either inconclusive, incongruous with each other, or demonstrate a narrowed focus on one piece of the biological mosaic of entangled life processes. Optimistic advocates of stem cells and exosomes are blindfolded dismissing the risk and deleterious effects of systemic incompatibility and immunorejection that ranges from low to severe, depending on manufacturing variability and individual differences. Then, there is the issue of marketing shadowing science and restricting the public's visibility down to a limited selection of trauma-based procedures.

A simple blood test comparing the young with the old will render aging synonymous with low-grade inflammation, hormonal imbalance, increased lipids and glucose, insulin resistance, visceral adipose tissue deposits, fatty liver and/or compromised function of more than one vital organ. Aging defects usually persist despite lifestyle changes and regular exercise. None of these systemic deficits can be reversed by trauma-based energy devices which have no evidence to definitively claim body synchronisation or rebalancing. Trauma-based procedures have not provided longitudinal studies proving wellness or results that do not rebound due to persistent metabolic issues and/or unsuppressed hunger. So how can these currently popular technologies claim that they offer a solution to the antiaging puzzle? Inner biological disharmony undermines immunity and breeds several diseases affecting both the human healthspan and lifespan. Instead of identifying isolated aspects of biological processes or studying different diseases separately, we can encompass a more comprehensive perspective of molecular interactions that visualize health and antiaging as an entangled multifactorial whole that requires equilibrium and harmonization to function optimally. This article examines different angles of antiaging research and mentions some underreported technologies that can synchronize the body to empower health and delay aging.

Keywords: Aging, DNA damage, exosomes, stem cells, genomic stress, epigenetic damage, stem cells, gene expression, proteostasis, hormonal balance, effortless exercise, resonance energy transfer, inflammation, radical damage

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Introduction

Antiaging research has branched out to multiple areas including studies on DNA integrity, gene expression, stem cells, exosomes, energy devices, effortless exercise, protein folding, and resonance energy transfer technologies that could be applied to antiaging. Sadly, the most popular methods and technologies are using the cloak of science to disguise marketing making claims that defy common sense. Furthermore, they double down on their claims by exaggerating the statistical significance of their results in paid journals.[1] Common sense dictates that repeated trauma increases inflammation which has been one of the most central causes of aging and disease. Rejuvenating and lipolysis lasers and RF technologies claim to reduce inflammation which is true in the surgery room when compared to knives but not when applied to older individuals who still look their age and remain overweight, despite the diminished wrinkles and limited fat loss that usually rebounds. Erasing wrinkles with fillers and Botox may give a superficial temporary solution to one's appearance, and a boost to one's self-esteem, but it does absolutely nothing, systemically, to help delay aging.

A number of scientists have postulated that genotoxic stress damages DNA signals contorting proactive messages that can order the self-destruction of deteriorated cells. If such cells are not eliminated the genome will become defective allowing the initiation of malignant processes.[2] In other words, senescent or malfunctioning cells must be terminated to avoid being transformed into cancers. It should be noted that human aging and cellular senescence are two different things. There is hardly any evidence that mechanisms involved in vitro observed cellular senescence are associated with in vivo human aging. The debate continues since observations of the aging process cannot be easily seen in vitro because in vivo cells are influenced by pH and temperature levels that cannot be replicated in vitro. There is also the issue of assumptions made during the in vitro research that

are contradicted by studies in vivo. For example the fact of telomere shortening has inspired theories suggesting methods to maintain longer telomeres as a method of delaying the aging process. However research studying mutations in the POT1 gene that sustains telomeres' length definitively shows that longer telomeres were correlated with a high incidence of both malignant and benign neoplasms that included 8 melanoma and seven thyroid cancers in the small sample of 15 subjects studied.[3–5]

The DNA has inherent mechanisms to combat genotoxic stress. Homologous recombination repairs double-strand breaks. DNA glycosylases can remove faulty DNA bases. Helix-contorting injuries are repaired by the extraction of nucleotides. The aging problem begins with the expression of pro-aging genes like, for example, those that trigger vascular diseases that affect the heart the brain or peripheral vessels like APOE, ACE, MTFHR and mutation at factor II and V genes.[6,7] However, there is no current popular technology that incorporates this information to intervene and delay aging.

Additionally, the same processes that are beneficial for the young, are deleterious to the old. The most pronounced example of this concept is inflammation that is necessary in acute injuries but becomes detrimental in chronic cases. Other such processes involve pathways such as the insulin, PI13, and TOR pathways that link development and aging, which eventually accelerate aging. This perspective conceptualizes aging as the aimless continuation of previously useful processes that should have been switched off upon completion but never did eventually harming health. An example of that is the importance of cellular division, which when persisting unmonitored and purposelessly, turns into cancer. In George Martin's wise words "The Brightest flame casts the darkest shadow".[8–10] This implies that, what is good for the young may be harmful to the old, a consideration that should be taken into advisement by device manufacturers who currently use the same methodologies for all ages. Again, all currently popular technologies are far from targeting signalling pathways with the exception of Resonance Energy Transfer (RET) technologies that have recently surfaced.[11–16] Resonance Energy transfer has not being utilized by any of the currently popular energy devices, including those claiming gene expression. Neither RET is largely applied to enhance differentiation of stem cells and or information transfer by exosomes as it should be highly recommended. Currently, risk-free aging delay still relies on procedures associated with exercise, body synchronization and healthy diet.

Chronic inflammation and aging

Inflammation is crucial for the organism's recovery after injury or infection. This same mechanism when persisting aimlessly undergoes an ugly metamorphosis, turning into low-grade chronic inflammation which is deleterious to wellbeing and is currently recognized as the centrepiece of aging and disease.[17–19] This persistent kind of inflammation is systemic. It is everywhere, unlike acute inflammation which is contained at the site of an injury. It is closely associated with metabolic dysfunction that increases adiposity and specifically visceral fat that is infested with inflammatory cytokines interconnecting, metabolism, inflammation and aging as a result of a general imbalance that involves hormonal disharmony, lipotoxicity and gut dysbiosis, which is defined as a dysregulated gut microbiome.[20]

Cell senescence is highly correlated with an increase in proinflammatory cytokines. Several investigators have postulated that inflammaging is the result of damaged or dead cells and cell debris that has not been removed by autophagy. Autophagy is a basic cleaning and recycling mechanism that eliminates or recycles dysfunctional components, which, when they accumulate, could suffocate and damage the system like piled-up garbage that contaminates the environment. The term is based on the Greek words "auto" meaning self and "phagy" which refers to eating something up. Autophagosomes carry the useless remnants of cells to the liposomes that digest or break down the junk parts of the cells to be eventually reused as building blocks. Despite its essential necessity, there is no known technology in the market today dedicated to increasing the process of autophagy. Lasers and RF corporations claim that they reduce inflammation but their claim appears to be limited to the site where the energy device was applied. There is no proof to suggest that they increase autophagy or that they reduce inflammation systemically.

Macrophages specialize in the detection and phagocytosis of harmful bacteria. They are implemented in wound repair due to their ability to secrete cytokines that are important for healing during acute inflammation. However, macrophages' persistent presence in chronic inflammation is systemically deleterious. The histocompatibility class-II protein is reduced on the macrophage cell surface receptors during aging. Macrophages are compromised along with the aging-related impairment of the toll-like receptor pathway that plays a role in how the innate immune system recognizes pathogen-related molecules. This systemic inability to recognize pathogens is accompanied by a reduction of interferons-y induced antigens that represent the first line of defence against viral infections. Macrophages are also connected to the nuclear factor-kb signalling pathway that upregulates the expression of proinflammatory genes, and proinflammatory agents like C-reactive protein and interleukin-6. Macrophage infiltration into adipose tissue triggers proinflammatory cytokines, resulting in chronic inflammation and metabolic problems. Visceral fat is infested in inflammation as it wraps itself around, suffocating and invading vital organs.[21–24] In conclusion, macrophages secreting proinflammatory cytokines can be useful under conditions of acute inflammation but turn into a deleterious event when aimlessly sustained and remains present in the wrong place at the wrong time.

Inflammation is the common denominator of both aging and disease affecting several biological events such as DNA damage and vital organs dysfunction. DNA damage activates inflammatory pathways such as cGAS-STING (cytosolic DNA sensing pathway) and the VF-kB (*Nuclear factor kappa-light-chain-enhancer of activated B cells)* signalling pathway. Both are involved in triggering cellular senescence, transposons that can alter the cells' genetic identity and persistent R-loops that act as a source of stressed-out, deficient DNA replication, genome instability and further DNA damage.[25,26] 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.

Exercise decreases inflammation and enhances health. However, it becomes progressively more laborious with age due to inherent fragility and deteriorated physical integrity. Few technologies have proven to reduce chronic inflammation by exercising the body effortlessly, balancing hormones and supplying the organism with the synchronicity necessary for optimal wellness. They are based on complex voltage-driven signals invented and composed at London University, which are accepted and integrated with the central nervous system by virtue of their compatibility with the CNS. The biological rule is that the body will discard any signals that are not in sync with the CNS as noise or even worse as damaging. The body will only allow access and utilize carbon copies of the signals transmitted by the Central Nervous System. The technology uses voltage to shoot

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through the skin, these CNS blueprint signals which were developed over a period of 47 years. The signals are carried to the brain by afferent nerves, triggering a brain-controlled series of organized full-body contractions accompanied by hormonal release that ultimately boosts metabolism, increases endogenous testosterone and growth hormones, while decreasing cortisol. Clinical studies have indicated a decrease in triglycerides, insulin resistance, and the very low-density lipoprotein, as well as a reduction of chronic inflammation as demonstrated by a decrease of the C-reactive protein. Additionally, they demonstrate suppressed cravings evidencing a regulation of ghrelin and leptin.[27–38] Again, despite their compliance with CE, FDA and IEC60601-1 standards, these handmade technologies are largely unknown due to the companies' focus on research rather than marketing.

Genotoxic stress, mitochondrial DNA damage and big data analytics

The DNA damage hypothesis, is one of the crucial aspects of the multidimensional instrumentation of what we lump under the simple term "aging." DNA undergoes a spontaneous decomposition due to its chemical instability triggering inevitable mutations that constantly undermine life, despite the multiple biological repair mechanisms available to the human body.[39] A number of external and internal sources can undermine DNA integrity. The DNA strands can be chemically modified or fragmented by exogenous attacks by free radicals which are the result of the superoxide residue as our cells metabolize oxygen into water in the mitochondria. Superoxide is transformed into hydroxyl radicals such as OH and H_2O_2 which are classified as reactive oxygen species (ROS). A number of studies on wound healing have explained the cellular repair observed to ultra-low microcurrents acting as mega-anti-oxidants that donate electrons to free radicals to transform them back into stable molecules and contain or even reverse this DNA damage at the molecular level.[40–43] Unfortunately, all these innovative devices are produced by small companies which are overshadowed by the large laser, RF, Botox and Fillers corporations that are blinding and brainwashing the public with glamorous ads making several unfulfilled promises. Moreover, it will be rather difficult for RF corporations to claim that they repair DNA because Animal studies have shown that exposure to 2.4 GHz of ratiofrequency significantly caused DNA damage to different tissues including the skin, kidney, liver and brain. Additional research conclusively postulates that RF signals at an average of at least 5.0 W/kg produce chromosomal damage in human lymphocytes.[44,45]

Although different from the exogenous DNA decomposing processes, endogenous ones can be equally deleterious to the genome. Endogenous and exogenous agents can interact to increase reactive species like aldehydes. DNA depurination can lead to mutations, as adenine or guanine are released from the DNA. There may also be hydrolytic deamination of the DNA bases when adenine and/or cytosine nucleotides lose amine groups.[46,47] Aldehydes are toxic agents that consist of a carbon atom that shares a double bond with an oxygen, a hydrogen, or another atom.

Mitochondria, the energy production factories of our bodies and the vital components of intracellular homeostasis, metabolism and calcium balance, have been widely implemented in the aging process. The mitochondrial protein synthesis apparatus is compromised during aging. The mutations of mitochondrial DNA are 10-fold more frequent that nuclear DNA. Mitochondria play a vital role in the integrity of the immune system and the declining t-cell function, hence the increased vulnerability of the aged to viral infections and a number of known diseases such as Diabetes, Cardiovascular disorder, cancer, and neurogenerative defects. All healing involves mitochondrial metabolic interactions with the nucleus and cross-talk with neighbouring and distant cells, utilizing signalling via metabokines which are involved in the regulation of systemic energy metabolism.[48–51] New developments in big data analytics can organize sensor data and offer a better understanding pertaining to the development of diagnosis and prognosis of several conditions.[52–54]

Gene expression and body rejuvenation

Gene expression procedures should take into consideration that health and antiaging benefits from gene expression depend on:

Qualitative factors

I. Which gene is expressed?

II. Does this gene have positive or negative properties or both? For example, the angiotensin-converting enzyme gene I/D polymorphism may have both positive and negative effects on the progression of cardiovascular disease.[55]

III. The position and context in which this gene is expressed. Context may lead to different interactive processes. Position may determine the advantages or disadvantages of a particular gene's expression. A gene's properties depend on the quaking (QK) locus of the gene or the position effects variegation that disrupts chromatin structure resulting in chromosomal rearrangements. The importance of positioning is described in Bedell et al.[56] article: "good genes in bad neighbourhoods".[56] The way a good person is corrupted when growing up in a bad neighbourhood; similarly, a gene undergoes mutations depending on its quaking locus. So the story does not end with gene expression but continues with what happens after within the genome of a particular individual.

Quantitative factors

Overexpression or under-expression of a gene. For example the zink metallopeptidase STE 24 (ZMPST24) gene is involved in the processing of Lamin A that cleaves progerin A. Failure to complete this cleaving process leads to the Hutchinson-Gilford progeria syndrome which causes premature aging. So one would think that ZMPST24 gene should have positive effects when applied to anti-aging and regenerative medicine. Yet, overexpression of the ZMPST24 gene and Lamin A/C mRNA are associated with chronic inflammation which, has been consistently found to speed up aging.[57,58]

Research has identified longevity genes such as the APOD, FOXO3 and CETP genes which, however, are only found in select 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.[59–67] But again, where is the so-called anti-aging technology that successfully reinforces the expression of these genes and gets true systemic rejuvenation results despite their overexpression, or the position effects variegation causing chromosomal rearrangements that could lead to problematic side effects?

Research by broadband light (BBL) did not document the expression of any of the longevity genes postulated by previous scientists. Instead, these investigators touted the expression of totally

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different genes focusing only on their positive characteristics while neglecting the potential harmful effects caused by the overexpression of these genes.[68–70] There is no indication of how this technology can prevent overexpression of any of the genes listed in their study, or any measure to calculate whether a particular gene is overexpressed, inevitably causing serious adverse reactions in an individual. The study is not without conflicts of interest. The researchers are affiliated with Stanford University, however, the research cited was financed by Sciton, a company that actually manufactures the BBL.

One of the "rejuvenation" genes listed in the BBL research is the ZMPST2, which, as previously noted, is correlated with chronic inflammation when overexpressed. Overexpression of the IGF1R, another gene the BBL researchers are reporting, is associated with the development of malignancies.[71] Nerve growth factor (NGF) is defensively increased in inflamed tissues.[72] Therefore, the presence of NGF4 could simply demonstrate the presence of inflammation after BBL treatments. Overexpression of EEF2 (another BBL cited gene) can promote the progression and enhancement of cancer cell growth in vitro and in vivo[73] -- a dangerous possibility that vulnerable patients undergoing BBL cannot afford. BBL research also reports increases in IL-4 and IL-13, both of which are associated with inflammation. CCL18 has been implicated in enhancing hepatocellular carcinoma cell migration, so it is unclear why it is classified as an antiaging gene.[74–76] In conclusion, BBL reports that their technology has rejuvenation results, however, the actual data examination may signify nothing more than the presence of inflammation.

Epitranscriptomics, the deep sequencing identification and mapping of RNA fragments has been successfully used in viral research.[77,78] The ageing epitranscriptome involves over 150 specific editing events. RNA modification can be beneficial in extending life, or dysfunctional resulting in neurodegenerative, cardiovascular, and autoimmune diseases.[79]

Genome Editing is currently used as a therapeutic intervention in the treatment of genetic disorders and will be probably extremely dangerous in the hands of optimistic antiaging doctors who may start experimenting on their patients in the absence of genetic training, education or experience. For this reason, the committee of the US National Academy of Sciences and the National Academy of Medicine have restricted genome editing to only the particular DNA sequence associated with the genetic disease.[80–82] Overall, further exploration of the vast variability of genes determining longevity is necessary before presenting this methodology as an antiaging solution. Research is ongoing in comparing the genetic profiles of individuals with longer lives with those who do not appear to have the same fortunate genetic predisposition. There is about 25-30% of a polygenic influence contributing to longevity that involves transcriptomic and epigenomic factors as described by biomarker and genomic studies.[83]

Aging is not the loss of proteins but the loss of protein homeostasis

The integrity of the Protein Network depends on the harmonious interaction of consonant, well matched protein signals that resonate to amplify systemic functionality within the stability of homeostasis. Loss of Proteostasis leads to disorganized protein networks resulting in intracellular damage that is characteristic of aging.[84,85] Loss of Proteostasis is defined by protein denaturation, misfolding and aggregation delivering nonsense signals like a senile brain. Proteins are the intelligence of the cells, and a misfolded protein is a scrabled brain.

Protein, synthesis and folding is one of the several steps determining both the connectivity and functionality of the protein network, its balance and Proteostasis.[86] Heat denatures proteins interrupting the Proteostasis network, an event that resembles the chaos caused when the internet that controls an entire city is down. Heat-producing devices such as lasers and RF commonly used in antiaging medicine denature proteins despite their widely known claims that they induce rejuvenation as a result of collagen production. Collagen is only one out of around 200,000 proteins that must interact harmoniously balancing each other. Collagen alone and without monitoring, participation or regulation from other proteins can produce nothing more than scars. All this should be obvious within the scientific community. Yet, all a marketing company has to say to get everyone's blessing is that their device increases collagen. Either there is a false assumption that collagen does not need to interact with other proteins to delay aging, or there is a misperception that collagen must be the only protein that matters, like the Royal Highness in charge of all other proteins. There is no logical reason to ignore all other 199,999 proteins or believe that the mere increase of collagen will magically increase all other components of the complex Proteostasis network. It is this Proteostasis network that maintains the body's reparative mechanisms that can delay aging. If these trauma-based devices increase nothing else but collagen, and in light of research testifying that heat and radiofrequency denatures proteins, then one can legitimately ask whether the current state of the art in antiaging medicine creates the conditions that eventually speed up the aging process by progressively undermining Proteostasis.[87,88]

There is evidence that long-term radiofrequency radiation (RFR) exposure, which adversely affects organisms, deteriorates testicular functions. Misfolding or unfolding protein accumulation in the endoplasmic reticulum (ER) initiates an intracellular reaction known as ER stress (ERS), which activates the unfolded protein response (UPR) that disturbs Proteostasis.[89]

Is aging loss of stem cells or arrested differentiation?

The two main dangers with stem cell injections are:

I. Immunorejection, where the immune system rejects the stem cells implant – an event that is more frequent with stem cells' injection than vital organs transplants, like for example a heart. Some techniques utilize antibodies to block normal T-cell activation and reduce immunorejection. These win the battle over the immune system rejecting the stem cells since they increase systemic acceptance of the injected stem cells; but they lose the war by enhancing the probability of potential tumour formation as a result of paralyzing the immune soldiers.

II. Tumour formation is a result of undifferentiated cells being lumped together without specialization. Cells must differentiate to be utilized by the body. Differentiation determines the specialization and organ category that these cells form, such as skin, bone, muscle, blood, immune cells, etc. Arrested differentiation leads to uncontrolled proliferation which results in the formation of malignancies. A cancer cell is unable to differentiate and therefore it never loses its growth potential. A cluster of cells with no specific meaning that assigns it a specific category within an interactive system obstructs rather than facilitates the cellular network. Cells that eventually become cancers are disorganized by free radicals like superoxide that prevent the normal process of differentiation from occurring.

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Cellular differentiation depends on a higher number of mitochondrial differentiation-promoting activity, and a lower number of nuclear differentiations that pause activity. Embryonic stem cells (EMCs) have a low mitochondrial content resulting in a low ratio of mitochondrial/nuclear differentiation. Therefore, their differentiation potential is compromised.[71–73] These facts render the risks of injecting EMCs rather high, especially if the procedure is for antiaging purposes, rather than being a necessary intervention to repair damaged tissues in cases where there are limited or no other therapeutic avenues.[90–92]

Mesenchymal stem cells (MSCs) are less versatile than EMC's but relatively safer. However, MSCs have limited clinical usefulness due to cellular senescence that impairs their differentiation potential. With the process of differentiation blocked, proliferation increases aimlessly and uncontrollably, forming clusters of undifferentiated cells or, in other words, tumours. Furthermore, the MSC's phenotype can be affected and compromised by the donors' heterogeneity, the culture condition, and the cell passage in the body.[93–95]

Is aging the absence or presence of exosomes carrying damaging signals?

The Nobel Prize 2013 was given to Rothman, Schekman and Südhof for pioneering the understanding of the organization and regulation of our cellular transport system.[96–98,100–102] These discoveries brought into light the exosomes as important messengers of genomic information that includes RNA, DNA and protein signals.

The complex cargo of exosomes is readily accessible via sampling of biological fluids (liquid biopsies). Exosomes are involved in complex intracellular pathways and have been used as biomarkers, cell-free therapeutic agents, drug delivery carriers, exosome kinetics, and cancer vaccines. Researchers have triggered exosomes' secretion out of engineered stem cells that have bone regenerative effects as an alternative to gene therapy.[103–106] Other investigators have looked into exosomes derived by mesenchymal stem cells[107] and have found that MSC's exosomes are instrumental in deleterious processes such as tumorigenesis, angiogenesis and metastasis; as well as, in other cases, being involved in suppressing tumours. Once again, as with gene expression therapies we have a hit-or-miss outcome in using exosomes that may suppress cancer or help it spread and metastasize.[108–112] Exosomes have been successfully used to repair both acute and chronic kidney injury.[93] This therapeutic outcome is often compromised, however, by the inherent variability of different labs in terms of the purification and manufacturing of exosomes.[94–96]

Protein signals, metabolites, and nucleic acids delivered by exosomes into recipient cells effectively alter their biological responses. Such exosome-mediated responses can be healing or the exact opposite: They can promote disease and/or speed up aging. Despite the exosomes' miraculous effects on several diseases, including cancer where exosomes are also used as a vaccine, there is clinical evidence that exosomes may promote viral infection by enabling the spreading of a virus into the body.[97–101] Viruses can use exosomes like a "Trojan horse" to gain access to our cells. It has been proposed that multiple viruses may package within exosomes, a process that would promote multiplicities of infection and viral genetic cooperativity. Recent studies have shown that exosomes released from bacteria-infected macrophages are pro-inflammatory, ultimately increasing chronic inflammation.[102–109]

Exosomes have opened new horizons in exploring and understanding cellular communications and have offered us the opportunity to develop new methodologies for treating different diseases. They have been welcomed by regenerative and anti-aging medicine, often without asking questions, and without examining the potentially harmful consequences and unwanted side effects. Understanding the advantages and dangers of exosome injections is crucial before adopting and applying exosome treatments in antiaging and regenerative medicine.[110–125]

Cracking the code for proteins' amazing structures

The Nobel Prize of 2024 In Chemistry was given to Baker, Hassabis and Jumper for developing an AI model that predicts the sequences of amino acids composing the three-dimensional structures which determine the functions of around known 200,000 proteins.[126–130] David Baker succeeded in using amino acids to build entirely new proteins that can be used as vaccines, pharmaceuticals etc.[131–135] As previously stated, proteins represent the intelligence of the cells. They sense, they act, they function as hormones, neurotransmitters, signal detectors, antibodies, biochemical catalysts, enzymes, etc. They are the managers of our biological factory that sustains life. Proteostasis, is the harmonious balance of proteins organized in configurations that reinforce immunity and enhance wellness. The centrepiece of antiaging medicine, collagen, is a protein. Collagen is only one out of the 200,000 known proteins that control aging and disease, so, as previous stated, the collagen popularity is greatly exaggerated.

The 2024 Nobel Prize fascinating research on proteins opens new horizons in antiaging and regenerative medicine and at the same time, it opens Pandora 's Box. It is predicted that in the next few years protein replacement therapies will flood the antiaging market, used by everyone, with or without a background or experience in protein folding and protein interactions and communications, and with very little concern regarding Proteostasis, the way stem cells boomed uncontrollably, without a deeper understanding of how proliferation without differentiation can be a health hazard; and the way exosome injections are currently filling up the market posing as the all-in-one solution of regenerative medicine, despite warnings for long term side effects and other potential health dysfunction.

Conclusion

Both repair and damage within the human body are initiated and progress at the molecular level which should be the focus of exploration and is now becoming the target of new interventions. Molecular mechanisms routinely go forward and backwards in time, like for example, free radicals that turn back into stable molecules by the addition and rebalancing of their electrons, or the main currency of energy production, ATP, that reverses itself into ADP with the subtraction of one phosphate and further down into AMP, before it can progressively be retransformed into ADP with the addition of a phosphate, and further on into ATP with the addition of a second phosphate. These simple observations reveal that time reversal occurs routinely in biomolecular dynamics. Yet, to date, time reversal has been proven to be impossible in whole entities. You cannot reverse the fate of a failing heart – you need a heart transplant to replace it. Neither we can go back in time or transfer ourselves to the future despite Einstein's perspective of conceptualizing time as a fourth dimension that can go forward or backwards, as it happens in three-dimensional space. Time cannot go backwards in our world because of the increased rate of entropy that determines progressive deterioration of life. Time cannot be reversed because the whole is a Gestalt that is more than the sum of its parts. A Gestalt has been developed as a result of resonating parts which have amplified and given life to a new entity that is different and no longer represents any of its parts, so in that sense it is irreversible. Vital organs are Gestalts. They consist of billions of

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cells none of which can in itself replace the entire vital organ. A person is also a Gestalt that consists of trillions of cells none of which can in itself replace the person. Proteostasis, hormonal balance and systemic synchronization are Gestalts of resonant processes that have been added or multiplied to form a new entanglement that surpasses and no longer exists in any of the processes composing it. The necessity of any group of processes to be resonant in order to form a Gestalt offers both restrictions and a new perspective to understand health and aging. In a nutshell, health is the result of molecular resonance leading to systemic balance. Illness is the conflict of elements that are not resonant forming dissonant wholes that cancel each other out. We need methodologies and technologies that are designed to synchronize and incease resonance in the body, because it's this synchronization and biological harmony that protects wellness, prevents illness and delays the aging process.

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Conflicts of interests

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