Eur J Transl Myol 35 (2) 13540, 2025 doi: 10.4081/ejtm.2025.13540

Longevity concept by regenerative medicine methods synergy: exosome therapy, functional medicine, and advanced multi-wavelengths laser therapy

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Abstract

Regenerative medicine is one of the most important branches of medicine today and in the future and brings together all the methods to stop or even reverse the aging process. Regenerative medicine may include cellular therapies such as stem cell therapy or extracellular vesicle therapies such as exosomes and growth factor therapy. It may also involve the use of Photobiomodulation (PBM) and functional medicine treatments targets on mitochondrial medicine, to control the aging process. In this article, we have discussed the role, importance, rationale, overlap, and synergy of the joint application of these methods. Combining these regenerative medicine approaches can achieve better results in various medical indications. For longevity, any autoimmune disease, chronic disease, especially in elderly patients, this recommended combination seems to be very critical, for a higher survival rate in cell therapy methods. It is like a plant growing process that requires good quality seeds (cell therapy), light (targeted laser therapy) and good soil (functional medicine).

Key Words: longevity, extracellular vesicles, exosome, stem cell, interstitial laser therapy, iv therapy, functional medicine.

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Aging is considered as a decline in healing and regeneration potential in cellular and sub-cellular level.[1] Although various hypotheses have been proposed to explain the cellular and molecular mechanisms of aging, recent studies increasingly clearly indicate that aging is caused by the accumulation of molecular damage, thereby leading to a unified theory of aging.[2] Among the reactions that contribute to this damage, reactions of free radicals and other reactive oxygen species are the main cause, in addition to reactions of metabolites such as reactive sugars and aldehydes as well as spontaneous errors in biochemical processes.[1,2]

All aerobic organisms are exposed to a common oxidant, oxygen. Organic compounds and the structures that make them up are thermodynamically unstable in an oxygen-containing atmosphere. Molecular oxygen, in its elementary triplet state, is quite unreactive due to spin limitation.[3] However, the formation of free oxygen radicals and other Reactive Oxygen Species (ROS) opens the door to harmful oxidative oxidation reactions. Seen from this perspective, the "Free Radical Theory of Aging" (FRTA), now commonly known as the oxidative damage theory of aging, appears to address an important aspect of destabilization. Intrinsic biological determination of living systems.[4] The basic idea of FRTA is that free radicals and other ROS, inevitably formed during metabolism and by the action of various exogenous factors, damage biological molecules and accumulate in them. This damage is responsible for age-related diseases and aging.[4,5]

Other concepts related to aging emphasize the development of DNA damage and repair theories. DNA damage is thought to contribute to the aging process because there is a positive correlation between DNA repair capacity and longevity,[5] however, it is no longer considered the only potential candidate to explain aging. As a promising modified successor, the free radical theory[6] has become one of the most widely accepted hypotheses about the mechanism of aging. As we age, the release of stem cells into the bloodstream decreases,[7] And as we have studied in many studies, aging is associated with moderate amounts of oxidative

stressors and, at the same time, a decline in metabolism. On the other hand, we found that this is associated with DNA damage and inflammation.[8] In chronic diseases and aging, we have all these pheromones together, so to prolong life we need a holistic approach. We can see that there are many similarities between laser therapy, exosome therapy and functional medicine, in which medicine exerts the power of combining all the similar effects of the mentioned methods. Accessment in treatment, longevity, control, rehabilitation, and aesthetics.

Functional medicine and longevity

Reactive Oxygen Species (ROS), the most abundant free radical in cells, covers a wider range. All highly reactive molecules containing oxygen can be classified into this category. ROS are unavoidable products of normal intracellular metabolism.[9] They play an important role in cell differentiation, proliferation, and host defense responses. However, their bad reputation is overwhelming. Various cellular components are thought to be damaged by oxygen-derived free radicals, of which lipid peroxidation, DNA damage, and protein oxidation are perhaps the most severe. ROS can cause lipid oxidation in cells.[10,11] Polyunsaturated fatty acids, a major component of cell membranes, are susceptible to free radical attack because they contain many double bonds with extremely reactive hydrogen atoms. As a result, the structure is susceptible to attack by free radicals, especially hydroxyl radicals, which will lead to destruction of cell membrane permeability and, ultimately, cell dysfunction. ROS can also damage DNA.[12] ROS-induced DNA damage mainly includes strand breaks, cross-linking, base hydroxylation, and base excision. Induction of this DNA damage will lead to mutations and thus transformation, especially if combined with a deficient apoptotic pathway. ROS can also lead to protein oxidation in the body. Proteins in cells are also believed to be the main targets of free radicals, leading to protein denaturation and enzyme inactivation. Furthermore, the reactive protein derivatives produced can act as mediators that cause the spread of oxidative damage to other cellular components.[10,12]

After injection of stem cells and extracellular vesicles such as exosomes, they will be attacked by the immune system and cannot survive due to the level of oxidative stress in chronic diseases, especially in elderly patients. Therefore, prescribing patients to reduce oxidative stress levels before any cell therapy appears to be important.[13]

The two main antioxidant systems, namely enzymatic antioxidants and non-enzymatic antioxidants, work systematically to eliminate free radicals.[14,15] The antioxidant enzyme system includes superoxide Dismutase (SOD), Catalase (CAT), Glutathione Peroxidase (Gpx) and Glutathione Reductase (GR) that protect the cells against ROS in vivo. There are two main types of SOD.[16] One of them is CuZnSOD (SOD1), which exists mainly in the cytoplasm, with copper and zinc present in the active site. The other is MnSOD (SOD2), located in the mitochondrial matrix, manganese is present in the active site. They can catalyze the decomposition reaction of superoxide anion radicals into H2O2, which will then be converted into water and oxygen by CAT or GPx.[16]

The non-enzymatic antioxidant system acts as a second defense system against free radicals. Non-enzymatic antioxidants can not only provide direct protection against oxidative damage but more importantly enhance the function of endogenous enzymatic antioxidants by synergistically scavenging free radicals due to reaction.[17] Vitamins C and E are the most well-known antioxidants in this category. However, a recent study shows that under certain circumstances, they can act as antioxidants.[18] In addition to vitamins, there are many small molecules that act as non-enzymatic antioxidants, such as phenolic compounds, flavonoids, and carotenoids found naturally in foods. Q10 (ubiquinol formulation) and reduced lipoic acid as well as melatonin are also effective antioxidants. Some researchers have shown that introducing antioxidants into cells or creating new antioxidants could be a breakthrough in regulating antioxidants against aging and longevity.[19] If mitochondria are the main source of ROS in cells, then antioxidants targeting mitochondria may be more effective than traditional antioxidants.[20] This idea is the basis for the synthesis of positively charged derivatives of plastoquinone and other antioxidants that are retained in the mitochondria due to the high negative potential of the inner mitochondrial membrane. This appears to be more important in chronic inflammatory diseases in elderly patients.

Stem cell and exosome and longevity

Considering to their self-renewal ability, exogenous stem cells can regenerate various tissues after damage.[21] Mesenchymal stem cells (MSCs), due to their ease of isolation, culture, and low immunogenicity, are the most studied cell type for application in clinical indications.[15,22,23] Historically, the main hypothesis was that stem cells must be able to integrate into damaged tissues and regenerate them through asymmetric division. However, more recent studies have shown that allogeneic MSCs have limited ability to integrate into tissues, as typically less than few of transferred cells survive for more than a week.[24] Despite these facts, MSC therapies have been investigated to be beneficial in many pathologies and enhance the regeneration of several tissues, suggesting that the most significant effects of these cells are mediated by paracrine. Therefore, MSC secretions have been positioned as a potential therapy for tissue repair and regeneration, such as exosomes.[25]

Exosomes are nanovesicles containing growth factors, secreted by stem cells from different sources, that can be used in regenerative processes.[26] The most widely used source in recent studies is MSC, perhaps due to their safety, simpler isolation, and cultivation techniques. The site of injection of exosomes varied from study to study, with the majority injecting them intravenously or topically when possible. One of the most evolutionarily conserved mechanisms for controlling aging and longevity is metabolism, mainly through several pathways involved in nutrient sensing and growth, e.g. insulin/IGF-1, mTOR, AMPK, etc.[21,25-27] These pathways have been shown to have important effects on longevity and health (*i.e.* calorie restriction or

mTOR inhibitors). Exosomes have been shown to induce profound metabolic changes in recipient cells; for example, exosomes from obese mice can increase insulin resistance and dyslipidemia in healthy mice through miRNA transfer. Additionally, miRNAs that undergo age-related changes in plasma exosomes are important regulators of these metabolic processes.[27]

Exosomes are double-layered lipid vesicles released by cells and contain a multitude of molecules considered responsible for their role in cell-to-cell communication, through the exchange of proteins, nucleic acids, or lipids. The use of exosomes adds several benefits over the use of stem cells to enhance tissue regeneration. Exosomes are more stable, have no risk of aneuploidy, are easier to penetrate, and have a lower rate of immune rejection. Exosomes from several types of stem cells have demonstrated the ability to enhance regeneration of various tissues after damage, such as the kidney, liver, heart, or brain.[26]

As many studies showed, aging is characterized by a loss of tissue regeneration, associated with a decrease in stem cell secretion and their ability to heal and repair. By aging, all stem cell in the adult body loses the ability to regenerate properly, both under basal conditions and after injury, with a lower number of potential divisions.[25,28,29] As aging progresses, progenitor cells responsible for regenerating damaged tissues acquire molecular characteristics that affect their regenerative ability, such as accumulation of DNA damage, telomere shortening or accumulation of both oxidative and inflammatory factors. Exosomes derived from stem cells and other cell types are currently being studied as potential regulators of many aging-related processes, such as cellular aging, oxidative stress accumulation, DNA, and telomere dysfunction, autophagy, immune imbalance, chronic inflammations, and metabolic disorders.[30]

One of the most important effects of exosomes is their potential role in modulating effects, such as on the immune system since exosomes from damaged cells often activate the immune system, leading to the release of inflammatory factors. On the other hand, exosomes are now considered important anti-inflammatory and immunomodulatory factors. During aging, an imbalance between pro-inflammatory and anti-inflammatory factors occurs, leading to the accumulation of pro-inflammatory factors in the extracellular environment that accompanies normal aging and is associated with to some age-related diseases. Exosomes may counteract the aging process by increasing anti-inflammatory molecules and decreasing inflammatory cytokines associated with aging, such as IL-6, IL-1β or TNF-α.[31-33]

By applying exosomes to damaged tissue or injecting exosomes into veins, we can balance the immune system, balance the metabolic system, increase the ability of the body's stem cells, bring many growth factors and anti-inflammatory factors into the body and target tissues, leads longevity.

Laser therapy and longevity

These mitochondria, our cells power houses, are marked by a relative enlargement of surface of the mitochondrial cristae due to activation of the respiratory chain and ATP-synthesis. One of the most important of low-level laser therapy or photobiomodulation (PBM) is mitochondria complexes. Also, there are hundreds and thousands of studies proves that PBM can active more than hundred genes related to healing processes in body.[22,34,35]

Photobiomodulation has an effect that can accelerate the healing process because it improves cell viability through stimulation of photoreceptors of mitochondria and cell membranes as well as ATP production. It can also play an important role in promoting cell proliferation, differentiation, and migration, as well as restoring cell metabolism.[13,23] Different mechanisms of action of PBM therapy in irradiated tissues have been identified, including regulation of histone acetylation and NFκB expression, some signaling activation such as ERK, SIRT1, PI3K/AKT and NF-Kb, which releases growth factors, stimulates extracellular matrix production, reduces inflammation, promotes platelet activation and aggregation, accelerates cell proliferation and migration, improves cell activity and survival, improves antioxidant capacity, preserves mitochondrial homeostasis, and promotes mitochondrial biogenesis and turnover.[13]

PBM may also influence stem cells and their proliferation, differentiation, and migration. In addition, PBM is also involved in the regulation of ROS, being able to enhance ROS for immune system signaling, but reduce it in stressed cells. In general, PBM, due to its effects, can improve the adaptive capacity of cells to cope with cell damage during disease development.[36] Therefore, this type of therapy may allow the development of new clinical approaches and combinations to achieve better results in treatment procedures.[37]

PBM has immunomodulatory effects like exosomes. Today, instead of using red and infrared wavelengths, a new form of photobiomodulation is identified using different wavelengths activated in the mitochondrial respiratory chain.[13,21,22,38] According to many studies, most of these elements only use red and infrared wavelengths. The reason is that these wavelengths can penetrate the skin through transdermal irradiation, which is the concept of the conventional form of PBM.[22] There are different types of chloroform in the body and these chloroforms have different properties and can play an important role in the regeneration process. The mitochondrial respiratory chain is one of the most important photo-bioregulatory receptors. Complex I of the mitochondria is the vitamin NADH which absorbs the blue wavelength, complex II of the mitochondria is riboflavin which absorbs the blue wavelength, complex III is coenzyme Q10 (ubiquinol) which absorbs the blue wavelength, the green wave and the complex IV and V complexes absorb red and infrared light.[22,39,40] Therefore, the use of different color properties increases the effectiveness of laser therapy and photobiomodulation. When laser treatments are performed, most laser treatment components only work at these wavelengths, eliminating the other properties of green and blue wavelengths in the mitochondria, but when they are used by tissue (interstitial), blood vessels laser irradiation (intravenous), intra-articular laser beam and by applying different laser fibers and applicators to the body.[41,42] Other

specific wavelengths and other chloroform substances can be used in the body, such as red blood cells, white blood cells, elastin, hemoglobin, and collagen, each of which has specific receptors to produce the property of having the strongest regenerative force in tissues.

Discussion and Conclusions

There are many different concepts of aging, such as the free radical theory of aging (changes in antioxidant/antioxidant balance leading to increased oxidative stress), functional dysregulation cells, metabolic impairment, and mitochondrial dysfunctions, can lead to impaired immune function, and increase the risk of morbidity and infertility and many other diseases.[13,21,22,43] Many methods can combat these phenomena and are applied as complementary, modern, or regenerative medicine, such as stem cell therapy, exosome therapy, advanced laser therapy and targeted IV therapy as presented in Figure 1.

Exosomes, due to their regenerative and immunomodulatory properties, are considered as a cell-free therapy that has demonstrated significant effects in preclinical models

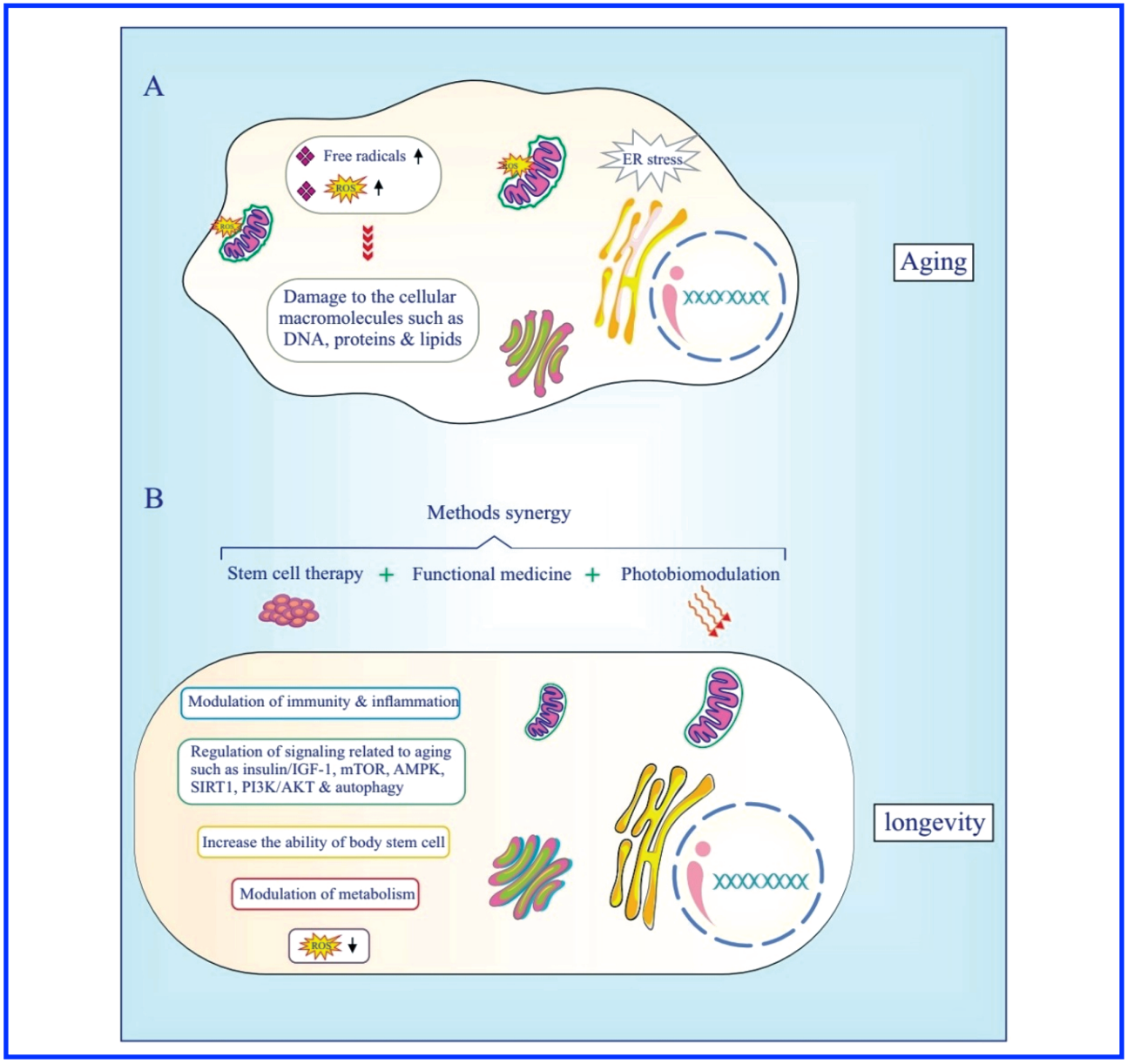

Figure 1. *By Aging, causes of lack of energy supply, lack of local blood circulation, high oxidative stress parameters in the cellular level, high nitric oxide and ROS levels, reduced immune system signaling and reduced regenerative mechanisms in the body lead to loss of ability. PBM, and functional medicine can counteract all these phenomenon and stem cell and exosome can plays their role, causes longevity.*

of several age-related diseases and tissue regeneration.[25,26] Exosomes not only have beneficial effects on disease but have also been shown to regulate many processes associated with aging, with a marked effect on the regenerative capacity of tissues. Several parameters can affect aging, such as parabiosis, dietary restrictions, mTOR inhibition, etc. In this regard, many proteins, miRNAs, and lipids have been proposed in various studies. In preclinical studies, miRNAs are probably the most studied factors because they can regulate many different pathways; however, some studies show that miRNAs are minor components of exosomes with a very low ability to enter target cells.[26] The main challenge of cell therapy approaches such as exosome injection, either topically or intravenously, is their potency to act. As many studies have shown, exosomes can stimulate circulating MSCs. For any healing and better survival rates at the cellular level, we need healthy mitochondria in a suitable environment. This means we need to reduce ROS and other chronic inflammatory parameters, while nourishing healthy cells and their mitochondria.

NADH-ubiquinone oxidoreductase or complex I, ubiquinone-cytochrome c oxidoreductase or complex III, and cytochrome c oxidase or complex IV are the three-electron transfer chain proton pump complexes of the mitochondria.[30] This complex absorbs blue range wavelength from the light. Mitochondrial complex II or succinate dehydrogenase does not pump protons but helps reduce ubiquinone. Complex I, NADH-Dehydrogenase (B3) is chloroform with UV and blue frequencies. Succinate dehydrogenase II complex is chloroform blue/green, and riboflavin (B2) is chloroform blue/UV-A. Complex III, Cytochrome-C-Reductase is chloroform with green/yellow frequency. Complex IV chloroform, a copper-dependent cyclooxygenase, has a red/NIR wavelength. And complex V combines magnesium, red chloroform and the infrared wavelength of ATP-Synthase. As you can see, several vitamins, including B2, B3, ubiquinol, copper and magnesium, key components of all regenerative processes, are linked to mitochondrial health.[44,45]

Therefore, all studies show that mitochondria are characterized by minerals (vitamins) and are one of the main targets of laser and PBM therapy, and on the other side, highly purified exosomes, stem cells contain many growth factors that will act function perfectly if their mitochondria function well.

Aging is the most important factor in the development of many of the diseases that affect us and is the main cause of disability and death in most countries. The use of treatments that target the causes of aging at the cellular and molecular level is one of the most promising areas of research in medicine. Some of these processes will likely need to be targeted to treat age-related diseases. In this sense, exosomes have been shown to regulate a variety of cellular processes due to their ability to regulate intercellular communication. Since the effectiveness of these methods has been reported in many articles, these methods can be used to treat and control many diseases and considered as a longevity approaches. However, stem cells have mitochondria and cannot survive for several days without functional medicine and PBM support. Many diseases are related to the silent inflammation and metabolic diseases, and as they age, their metabolism slows down and they lose large amounts of growth factors, stem cells, and exosomes in within a few days, the rest is lost. By Aging, causes of lack of energy supply, lack of local blood circulation, high oxidative stress parameters in the cellular level, high nitric oxide, and ROS levels, reduced immune system signaling and reduced regenerative mechanisms in the body lead to loss of ability. PBM, and functional medicine can counteract all these phenomenon and stem cell and exosome can plays their role. More investigation is necessary to evaluate our hypothesis.

List of abbreviations

PBM, Photobiomodulation
ROS, Reactive oxygen species
FRTA, Free Radical Theory of Aging
DNA, Deoxyribonucleic Acid
SOD, superoxide Dismutase
CAT, Catalase
Gpx, Glutathione Peroxidase
GR, Glutathione Reductase
SOD1, CuZnSOD
SOD2, MnSOD
MSCs, Mesenchymal stem cells

Conflict of interest

The authors declare no potential conflict of interest, and all authors confirm accuracy.

Ethics approval

This article is a review article and don't need to ethic code. The study is conformed with the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights.

Informed consent

All patients participating in this study signed a written informed consent form for participating in this study.

Patient consent for publication

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Submitted: 28 December 2024.
Accepted: 20 January 2025.
Early access: 8 May 2025.