The role of peroxisome proliferator-activated receptor-coactivator-1 gene in skin aging

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Skin aging is a continuous process that exhibits fine and deep wrinkles, thin and transparent skin, loss of underlying fat, dry skin and itch, following decreased collagen and elastin synthesis. Both extrinsic and intrinsic agents are considered in the pathogenesis on skin aging. Extrinsic factors such as sun exposure, windy and dry weather, nutrition, and lifestyle may induce premature aging, toxic-free radicals, and reactive oxygen species due to decreasing normal function of mitochondria which play the major intrinsic factors in premature skin aging. One of the major genetic factors in mitochondrial function is peroxisome proliferator-activated receptor-coactivator-1 (PGC-1) gene. This factor could delay skin aging by increasing the mitochondrial biogenesis and replication and oxidative phosphorylation and so may induce free radical scavenging. This review is focused on intrinsic skin aging and the role of PGC-1 protein in decreasing effect of aging causes.

Key words: Free radicals, mitochondria, peroxisome proliferator-activated receptor-coactivator-1, replication, skin aging, wrinkle

INTRODUCTION

Aging is the loss of biological function and low fertility along with progressing chronological age that usually occurs after sexual maturation and continuous until death date. This process occurs throughout body and for everyone, but there are several ethnical-racial and personal differences. The initiation of senile process is different in various organs, for instance, brain in 20, bones in 35, heart in 40, and liver in 70 years of age.[1] Aging is caused by the accumulation of cell damages and nonrepaired cells which are an uncommon process between all species. Some types of damages are unavoidable such as ultraviolet (UV) radiation, free radicals, and genetic effects, and others involve environmental and behavioral influences.[2] The human skin is the outer cover of the body and largest organ of covering system as other organs emerge aging in the age of 25. The skin has multiple layers of ectodermal tissue and guards the underlying muscles, bones, ligaments, and internal organs.[3] This organ interfaces with the environment and plays a key role in protecting the body against pathogens and excessive water loss,[4] insulation, temperature regulation, sensation, and synthesis of Vitamin D and Vitamin B folates.[5] The skin has a surface area of between 1.5 and 2.0 m² and most of it between 2 and 3 mm (0.10 inch) thick. The average square inch (6.5 cm²) of skin holds 650 sweat glands, 20 blood vessels, 60,000 melanocytes, and more than 1,000 nerve endings.[6] Skin is composed of three primary layers: (1) The epidermis that enriches of keratinocyte, which provides waterproofing and serves as a barrier to infection (2) the dermis, which serves as a location for the appendages of skin and (3) the hypoderm (subcutaneous adipose layer).[3] There are two distinct types of skin aging: Aging caused by inherited genes that are called intrinsic (internal) aging, the other type of aging is known as extrinsic (external) aging. Intrinsic aging, natural aging process, is a continuous process that normally begins in our mid-20s with reducing collagen

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and production, and that enables skin to conserve its spring status.[7] The signs of intrinsic aging are fine wrinkles, thin and transparent skin, loss of underlying fat, dry skin and itch, inability to sweat sufficiently to cool the skin, graying hair that eventually turns white hair loss, and nail plate thin. In extrinsic aging, number of external factors acts to prematurely age our skin. Most premature aging is caused by sun exposure and other external factors such as gravity, sleeping positions, smoking, pollutions, and malnutrition.[8] Sun exposure each day over the years can cause photoaging that includes noticeable changes to the skin such as freckles, age spots, telangiectasia, rough and leathery skin, loose skin, actinic keratoses, and eventually skin cancer. Furthermore, repetitive facial exercise and movements actually lead to fine lines and wrinkles. Changes related to gravity become more pronounced as we age. The effect of gravity becomes evident in our 50s with skin's elasticity declines dramatically, drooping of the tip of the nose, elongation of the ears, falling off the eyelids, and disappearing of the upper lip too while the lower lip becomes more pronounced. Resting face on the pillow in the same way every night for years on end also leads to wrinkles called sleep lines. Smoking also accelerates aging to up to 4-fold due to accumulation of chemical toxic agents in the body.[9] Various attempts have been performed to rejuvenate and treat skin aging, but there is no any definite method because of its multifactorial nature. The skin anti-aging strategies attempted to reverse the dermal, and epidermal signs of photoaging and chronological aging can be grouped under the following approaches: Cosmetological care (daily skin care, correct sun protection, esthetic noninvasive procedures),[10] topical medicine agents or topical agents (antioxidants and cell regulators),[11] invasive procedures (chemical peelings, visible light devices, intense pulsed light, ablative and nonablative laser photo – rejuvenation, radiofrequency, injectable skin biostimulation and rejuvenation, prevention of dynamic wrinkles, correction of static, anatomical wrinkles, restoration [redistribution] of fat and volume loss, skin augmentation and contouring),[12] systemic agents (hormone replacement therapy and antioxidants),[13] avoiding of exogenous factors of aging (smoking, pollution, solar UV irradiation, stress), correction of lifestyle and habits (nutrition, diet restriction and alimentary supplementation, physical activity, control of general health), and preventive medicine.[14] For example, Nilforoushzadeh *et al.* studied twenty patients whose facial wrinkles and lines were treated by transplantation of autologous cultured fibroblasts. The mean of improvement at the 6-month follow-up was 41%, and this procedure showed that autologous fibroblast transplantation can be an effective procedure for correction of wrinkles and atrophic scars.[15] In addition, rejuvenate face skin and fat maintenance in the face can be maintained by autologous fat injection.[16] In other study, Nilforoushzadeh *et al.*

compared the efficacy of 50% trichloroacetic acid (TCA) solution and CO_2 laser for treatment of the atrophic scars due to leishmaniasis. The improvement of scar was 48.13% in the TCA group and 44.87% in the CO_2 laser group. Hence, Nilforoushzadeh *et al.* suggested the use of this treatment for correction of the atrophic scars.[17] Further, Ali *et al.* evaluated the effect of topical 5% TCA cream in the treatment of papulonodular leishmaniasis lesions. With considering the efficacy of TCA in decreasing the size of the residual scar and its low cost compared to other treatments, results suggested that 5% TCA cream could be considered an alternative modality for intralesional glucantime in the treatment of lesions.[18] Furthermore, chemical peelings such as tretinoin 1% have more efficiency than other topical therapies in the pigmentation.[19]

MITOCHONDRIAL THEORY AND OXIDATIVE STRESS IN AGING

One theory introduces the free radical or oxidative stress major contributor of aging proposes and longevity of the species.[20] Mitochondria are intracellular membraneous organs that have electron transfer chain and play important role in producing energy. The metabolic pathway in mitochondria includes attachment of free electrons to oxygen and is normally neutralized by hydrogen ion to form water. Sometimes, the process fails and the electrons do not attach to oxygen and instead, attach to other oxygen species, and make molecules such as hydroxyl, superoxide, and peroxide – collectively called reactive oxygen species (ROS). Aging is related with changes in molecular structure of DNA, RNA, lipids, proteins, and prostaglandins that all are stress oxidative target. In addition to oxidation, spontaneous errors and other modifications of proteins cause these changes and accumulation of these molecular changes, in particular, proteins, forms the basis of cellular aging.[21] In cells, antioxidant enzymes inactivate ROS; however, during skin aging, the effectiveness of endogenous antioxidant system is diminished.[22] Formation of ROS is an internal cause of skin aging as well as modern life has increased the number of toxic-free radicals that diet and environment are the most important. For example rancid fats, fats that have been heated to high temperatures, automobile exhaust and cigarette smoke affected skin aging. The skin has a complex defense system to deal with harmful environmental and chemical substances, but excessive exposure can overwhelm the system leading to oxidative stress and oxidative damage.[23] The mitochondria are the sites of the highest ROS production in the cell and exposing the mitochondrial DNA (mtDNA) to oxidative damage. Because of limit repair mechanisms available for mtDNA, the mutational rate of mtDNA is approximately 50 times higher than that of nuclear DNA, and accumulated mutations decline the normal function of

the mitochondria.[24] ROS not only induces DNA damage but also intracellular lipid peroxidation, gene expression changes and protein product. Further, replication is stopped and occurred transcription double-strand breaks, and ultimately, cell death.[25] Accumulation of mutations in mtDNA lead to decreased oxidative phosphorylation as well as an imbalance in the expression of antioxidant enzymes that resulting in greater overproduction of ROS.[26] Thus, malfunction of mitochondria contributes to skin aging, so ROS and mutations of DNA cause signs of aging including the development of fine lines and wrinkles, decreased or impaired barrier function, and loss of skin tissue which are direct consequences of the loss of mitochondrial enzymatic activity. Although a specific signaling cascade results in an increase in matrix metalloproteinase-1, which is necessary to recycle spent proteins or interstitial collagenase expression, this upregulation leads to the degradation of healthy collagen, resulting in cutaneous aging. Overall high-level ROS, DNA damage, and malfunction of mitochondria resulted premature cellular aging and skin aging.[27]

OTHER CAUSES OF AGING

In addition to DNA damage and role of ROS, another prominent cause of somatic damage is related to "reducing sugars," which react with carbohydrates and free amino groups, resulting in difficult-to-degrade ages. They accumulate in long-lived structural proteins, such as collagen and elastin increasing the stiffness of blood vessels, joints, and bladder and impairing function in the kidney, heart, retina, and other organs.[28] Other factor is telomere that acts as genetic biological clock and after about fifty divisions, a critical amount of telomere DNA is lost. The telomerase enzyme, which is present naturally in some mammalian cells, can compensate this lack of telomeres, and it suggested that telomerase can result in longer life in mice. Although there are concerns on its side effect in cancerate cells as well.[29] Recent research in 2003 points to another biological clock, which determines the lifespan of an organism. Indeed, accumulation of damaged proteins within the cell or breakdown in the proteins that control DNA replication and repair or damage in the DNA , are powerful forces in all cells that predetermine expiration date that called programmed age and it is noticed that about 80% of cancers are diagnosed in people over 55 years of age.[30]

AGING GENETIC

Longevity is known to be primarily a matter of environment such as diet and smoking. Genetics is thought to contribute to only about 25–30% of the variation in survival to 85 years of age. However, research in 2010 revealed that a cluster of 150 variants in DNA sequence can be used

to predict (with 77% accuracy) whether a person has the genetic wherewithal to live to 100 years old.[31] According to Richard Dawkins theory, our bodies are composed of genes that activate throughout our lifetimes, some when we are young, and others when we are older. Presumably, these genes are activated by environmental factors and the changes caused by these genes activating can be lethal. Therefore, to extend life, we should be able to prevent these genes from switching on, and we should be able to do so by "identifying changes in the internal chemical environment of a body that take place during aging. and by simulating the superficial chemical properties of a young body."[32] Another recent research on aging has identified a gene in the roundworm called daf-2 that mutation in this gene led to the lifespan of the organism is doubled. This daf-2 gene can be considered a "master gene" of aging because this protein can control the activities of many other genes and its expression gradually shuts down the cellular repair mechanism as we aged.[33] But biologists working with fruit flies activated a gene called peroxisome proliferator-activated receptor (PAPR)-coactivator-1 (PGC-1), which increases the activity of mitochondria and extends their lives by as much as 50%.[34]

ROLE OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-COACTIVATOR-1 IN MITOCHONDRIA FUNCTION AND AGING PROCESS

One of the most important factors in gene transcription process is functional connection between transcription factors and the general transcription apparatus that this connection is performed by coactivators. Coactivators are protein complex that increases the rate of transcription by interacting with transcription factors but does not itself bind to DNA in a sequence-specific manner. These complexes contain individual proteins that mediate docking on transcription factors and others that mediate necessary functions for transcription itself include modifications of histones by acetyltransferase activity, modification of histones by phosphorylation or methylation, and unwinding and remodeling of chromatin in an ATP-dependent fashion. Coactivator complexes have another enzymatic activity.[35] Studies of the regulation of the adipose cell lineage led to discover a coactivator with an amazing degree of regulation in different tissues and physiological states. This coactivator is PGC-1 that is a part of a small family of transcriptional coactivators, and its gene is located on four chromosome and codes protein 40 kDa. This protein has not enzymatic activity and is activated only with binding to transcription factors and uses src-1 and CBP/P300 proteins that have histone acetyltransferase activity.[36] PGC-1 is involved in multiple biological responses related to energy homeostasis, thermal regulation, and glucose metabolism. Most adaptive thermogenesis in small

mammals takes place in brown adipose tissue (BAT) that contains multiple small droplets of triglycerides and a high number of mitochondria. Their mitochondria contain a specific uncoupling protein-1 (UCP-1) that it is an essential component for cold-induced thermogenesis. UCP-1 gene expression is highly cold inducible through the activation of the sympathetic nervous system and is mediated by beta-adrenoreceptors and cyclic adenosine monophosphate.[37] Several activated nuclear hormone receptors play an important role in the differentiation of brown fat cells and in UCP-1 gene expression including thyroid hormone receptor, retinoic acid receptor 22, and PPARs (PPAR-α, PPAR-γ).[38] PPAR-γ has a key role in this differentiation. Although these data strongly support that this factor alone cannot determine diff erentiation and PGC-1 factor increases PPAR-γ function .So that this protein interacts with the nuclear receptor PPAR-γ, which permits the interaction of this protein with multiple transcription factors. Also PGC-1 can interact with, and regulate the activities of, cAMP response element-binding protein (CREB) and nuclear respiratory factors (NRFs). Transcription of PGC-1 is strongly induced in BAT in mice exposed to the cold.[39] Indeed, cold-induced PGC-1 expression strongly coactivates several nuclear receptors that bind to the UCP-1 enhancer that resulted to UCP-1 expression and mitochondrial biogenesis in BAT. Enhanced mitochondrial biogenesis is an important component of adaptive thermogenesis, especially in BAT and skeletal muscle, in which PGC-1 is highly expressed and inducible by cold or adrenergic stimuli. Exposure to cold temperatures induces mitochondrial proliferation.[40] Two novel transcription factors, nuclear respiratory factor (NRF)-1 and -2, bind to the promoter region of a broad range of mitochondrial genes encoded in the cell nucleus including β-ATP synthase, cytochrome-c, cytochrome-c-oxidase subunit IV, and mitochondrial transcription factor A (mtTFA).[41] PGC-1 dramatically induces gene expression for NRF-1, NRF-2, and mtTFA and physically interacts with NRF-1 and coactivates its transcriptional activity and activates mtDNA replication and transcription.[42] Whereas some cells such as epidermal cells covering the skin's surface are constantly replaced (2 weeks); now, if the skin is so young, why do not we retain a smooth complexion even into old age? The answer lies with the mtDNA, which accumulates mutations at a faster rate than DNA in the nucleus and its repair system is weak. These mitochondrial mutations are responsible for the gradual loss in mitochondrial function of skin cells and the quality of collagen (skin's scaffolding), which is why skin loses its shape and forms wrinkles. Finding ways to protect or repair mtDNA could significantly delay aging. In recent study, David Walker increased longevity of fruit flies, *Drosophila melanogaster*, with increasing PGC-1 expression within the fly's digestive tract. As it is mentioned with age, mitochondria become less efficient and less active that led to reduce all cellular functions and aging, respectively. David Walker discovered increasing PGC-1 gene activity in the intestine can slow aging, both at the cellular level and at the level of the whole animal and delays cell changes initiation with increasing mitochondrial function.[34] With regard to role of PGC-1 gene in different processes such as mitochondrial biogenesis and increasing oxidative phosphorylation, it seems that more induction, and high expression of PGC-1 gene can regulate mitochondrial synthesis and activity in cells such as epithelial cells, conserve structure and function of skin cell and delay their aging.

OTHER ROLES OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-COACTIVATOR-1

Furthermore, mitochondrial biogenesis, PGC-1 can increase longevity with contributing in function of different organs. PGC-1 is a potential target of cytokines such as interleukin-1 alpha (IL-1α), IL-1β, and tumor necrosis factor alpha that can activate the transcriptional activity of PGC-1 through direct phosphorylation byp38 mitogen-activated protein kinases that eventually increase respiration and expression of genes linked to mitochondrial uncoupling and energy expenditure.[43] Further, in heart relatively high levels of PGC-1, mRNA expresses that involve in genes regulation include several genes of the electron transport chain, mitochondrial biogenesis, and fatty acid β-oxidation. Massive overexpression of PGC-1 in the hearts of mice resulted in a large increase in mitochondrial biogenesis and a dilated cardiac myopathy.[44] Thus, PGC-1 could be a target for the development of novel therapeutic strategies to improve dysfunction in certain cardiac diseases. In addition, PGC-1 increases glucose uptake by increasing of mitochondrial respiration in skeletal muscle cells and also induces gene expression for the insulin-sensitive glucose transporter-4.[45] On the other hand, PGC-1 induces genes expression related to gluconeogenesis such as phosphorenolpyruvate carboxykinase, fructose-1, 6-bisphosphatase, and glucose-6-phosphatase and stimulates a 3-fold increase in the ability of hepatocytes to secrete glucose.[46] PGC-1 expression in liver is dramatically increased by fasting and is effective for stabling glucose level in fasting or diabetic, when exists low insulin or resistant to insulin, although insulin is a suppressor for PGC-1 expression.[47]

CONCLUSION

Aging is a collection of quite predictable diseases gradually caused by the deterioration of the body.[48] The skin is the outer covering of the body emerges aging in 25 age.[3] Skin aging emerges with declined collagen and elastin

production as fine wrinkles, loss of underlying fat, dry skin, itch, etc.[7] In addition to external factors such as smoking, pollutions, and ROS, oxidative damage involves in prematurely age our skin.[8] Mitochondria as source of ROS have weak repair system. Accumulation of mutations in mtDNA lead to malfunction of mitochondria that finally oxidative phosphorylation, antioxidant enzymes are decreased, and ROS levels and cell damage are increased. This malfunction results to skin aging and ROS exert aging signs, for example, fine wrinkles, loss of underlying fat,….[24,26,27] Proportion of genetics in longevity is thought to be only about 25–30%.[31,33] Researchers confirmed role of PGC-1 protein in increasing mitochondrial function and lifespan of fruit fly to 50%.[34] Effect of this gene was confirmed to connect transcription factors and the general transcription apparatus and increase transcription, as well as in processes such as mitochondrial biogenesis, thermogenesis,….[40] PGC-1 activate mtDNA replication and transcription by inducing and interacting with NRF-1, NRF-2 factors of mitochondria.[41,42] For healthy and youth, skin is necessary basement membrane (BM) be intact and functional to maintain normal protein synthesis; thus, now, some cosmetic ingredients also promote BM repair by increasing the synthesis of BM components, such as laminin 332, and Type IV and VII collagens, in the epidermis. [49] However, major cause of skin aging is malfunction mitochondria and with regard to positive and important role of PGC-1 protein in mitochondrial biogenesis in different organs such as skin; it seems that increasing of PGC-1 protein expression by different methods such as using of supplements can be effective in delay aging as various studies confirmed effect of supplements such as Panax ginseng root extract or pomegranate fruit extract in improving mitochondrial function by increasing key transcriptional factors: AMP-activated protein kinase, PGC-1 alpha, NRF-2.[50] Thus, more searches are required for PGC-1 expression and delay skin aging.

Conflicts of interest
There are no conflicts of interest.

AUTHORS' CONTRIBUTION

ShA, MAN and MA contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspect of the work.

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