Journal of Allergy & Therapy
ISSN: 2155-6121

Khorsandi et al.,, J Allergy Ther 2016, 7:6
DOI: 10.4172/2155-6121.1000245

Review Article Open Access

Personalized Medicine: Regulation of Genes in Human Skin Ageing

Danial Khorsandi[1,2*], Amirhossein Moghanian[1], Roya Nazari[3], Ghazaleh Arabzadeh[4], Sara Borhani[4], Mehdi Rahimmalek[4], Hadis Sabzi[5] and Niloofar Ziamahmoudi[6]

[1]*Harvard-MIT's Division of Health Science and Technology, Harvard Medical School, USA*

[2]*University of Barcelona, Spain*

[3]*Northeastern University, USA*

[4]*Department of Biotechnology, Isfahan University of Technology, Iran*

[5]*West Virginia University, USA*

[6]*Massachusetts Health and Science University, USA*

[*]**Corresponding author:** Danial Khorsandi, Harvard-MIT's Division of Health Science and Technology, Harvard Medical School, USA, E-mail**:** danialkh@MIT.edu

Received date: December 10, 2016; **Accepted date:** December 26, 2016; **Published date:** December 31, 2016

Abstract

As people grow older, the common conditions and developments that happen by aging are skin changes. For example, over period of time, the skin becomes drier and thin, and other changes will start to occur such as appearing spots, decreasing elasticity, increasing stiffening and appearance of wrinkles on skin. There are many medical procedures which can be helpful to mitigate skin changing process. Most of the commercialized cosmetic products have been created for the majority of customer's population. For instance, the use of many anti-aging creams may or may not prevent or even treat the changes of skin. Therefore, the effect of these products, and the reaction of the body is not the same for different people. The causes of this difference can be related to many parameters such as environment, nutrition, etc. Therefore, the human genome book can be the best source of finding the most accurate solution. The appropriate type of cream for an individual's skin type can be verified and used accordingly. Global gene expression profiling (commonly called genomics) is an approach that can be used for the identification of compounds for inclusion in cosmetic formulations that improve the appearance of aged skin. In this study, the evaluations of all genes and their related antioxidants, which lead to skin aging have been studied. The main goal is to match the appropriate medical procedure with the correct type of cream.

Keywords: Elasticity; Antioxidants; Aging; Transcriptomics; Keratinocytes; Pharmacogenetics; Homeostatic; Etiology; Microarray

Introduction

As people grow older, the common conditions and developments that happen by aging are skin changes. For example, over period of time the skin becomes drier and thin [1], and other changes will start to occur such as appearing spots [2], decreasing elasticity [3], increasing stiffening [4] and appearance of wrinkles on skin [5]. There are many medical procedures which can be helpful to mitigate skin changing process [6,7]. The most of the commercialized cosmetic products have been created for the majority of customer's population. For instance, the use of many anti-aging creams may or may not prevent or even treat the changes of skin [8]. Therefore, the effect of these products, and the reaction of the body is not the same for different people. The causes of this difference can be related to many parameters such as environment [9], nutrition [10], etc. Therefore, the human genome book can be the best source of finding the most accurate solution. The appropriate type of cream for an individual's skin type can be verified and used accordingly. In this study, the evaluations of all genes and their related antioxidants which lead to skin aging have been studied. The main goal is to match the appropriate medical procedure with the correct type of cream.

History of Aging

Aging process is defined as a process, which is intrinsic to the living system, and individual events that does not occur suddenly [11]. It is also described as deleterious in the sense that they decrease the ability of an individual to survive [12]. Failure in several physiological functions is classified by aging that leads to an increasing probability of death. One of the obvious signs of human aging is the changes in physical appearance [13], such as wrinkled skin as well as the dysfunction of interior human body organs, such as a decreasing inconsistent filtering of kidneys [14], the digesting system [15] and muscular strength [16]. Over a certain period, human bodies will go through many changes and adapt to multiple environments. The environment is a very hazardous nature and over time, human bodies will be more prone to many different types of diseases. There might not be a guarantee in medical resolutions for such diseases other than living a healthy lifestyle [17]. In a broadest sense, the change in the central information system is the mechanism of genetic aging [18]. The important cause of genetic regulation of aging can be related to the continuum of development and the gradual alteration of vital areas of the genome [18].

Natural aging process and external aging process are respectively called intrinsic and extrinsic aging that are considered as two essential processes that induce skin aging [6]. Genetic backgrounds combined with a long period are influential to intrinsic aging. Photo damages such as wrinkles, pigmented lesions, patchy hypo-pigmentations, and actinic keratosis develop an extrinsically aged skin [19]. Slowed

collagen, elastin production, slowed exfoliation, and decreased cellular regeneration are some examples of intrinsic aging that progress skin aging [5] while severe physical and psychological stress, alcohol intake [20], environmental pollution [21], smoking [22] and exposure to ultraviolet (UV) irradiation [23] are some instances of extrinsic aging that develop skin aging growth [17].

Causes of Skin Aging

There are several skin aging factors that contribute to age-related changes including oxidative stress theory of free radicals, the mitochondrial dysfunction, UV radiation and other mechanisms that may or may not influence skin changes acceleration [24]. The accumulation of oxidative cellular damage, which was suggested by the former factor of aging mentioned above is the main contributor to the aging process. It is also considered as one of the key determinant of longevity of the species [25]. Damage from free radicals shown by multiple reactive oxygen species (ROS) is influential evidence of aging [25–27].

UV induced by ROS and radiation of sunlight can cause pigment changes such as liver spots, thickening of the skin, noncancerous skin growths, and loss of elasticity [28].

Environmental Aspects of Skin Aging

The skin plays an important role as a protective barrier between the internal organs, the body, and the environment [29]. Human skin has a very broad and complex defensive system dealing with harmful and hazardous chemicals in the environment. However, excessive or chronic exposure will overwhelm the system and lead to oxidative stress and damage. Incontrovertibly, human skin is the most important interface between humans and their chemical, physical, and biologic environment [30]. Protecting humans from the environment, controlling body temperature, fluid and electrolyte balance are some obvious skin performances.

Accumulation of insults or damages created by the environment is the key factor of aging according to stochastic theories. The most obvious effect of environment on skin aging is obtained from solar UV irradiation [31]. UV exposure is one of the most reasons of skin aging that boosts ROS generation in cells. Wrinkles and atypical pigmentation are the most common examples of skin aging that have been generated by intracellular and extracellular oxidative stress initiated by ROS [32]. The oxidative stress in the skin also causes multiple cellular damages, in the present of UV radiation, by generating O_2, H_2O_2 (Equation 1), OH radicals (through Fenton reaction) (Equation 2) [33,34].

Ames and others showed that ROS and free radicals such as superoxide anion ($\bullet O_2-$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($OH\bullet$), and singlet oxygen (1O2) are the main causes of aging process and mitochondria is considered as the vital source of these two reasons that consumes 90% of oxygen in aerobic living organisms (Equations 1 and 2) [35].

The consumption of O_2 by mitochondria is the result of normal aerobic respiration and the reduction in forming steps to produce water presented in the (Equation 3) [36].

$H_2+O_2H_2O_2$ (1)

$H_2O_2+Fe^{2+}+H^+Fe^{3+}+OH^\bullet+H_2O$ (2)

$$O_2 \xrightarrow{e-} \bullet O_2^- \xrightarrow{e-} OH^\bullet \xrightarrow{e-} H_2O \rightarrow (3)$$

Equation 3: Normal metabolism of oxidants- The formation of $O._2$, H_2O_2, and .OH occurs by successive additions of electrons to O_2.

Methods

Aging genomics

Global gene expression profiling (commonly called genomics) is an approach that can be used in the identification of compounds for inclusion in cosmetic formulations that improve the appearance of aged skin. For example, transcriptomics profiling of photoexposed and photoprotected skin from women in their 60s compared with those in their 20s has led to identification of age-related alterations in lipid synthesis, epidermal differentiation, oxidative stress and extracellular matrix. This understanding has proven useful in the identification of cosmetic compounds.

Studies have shown that human lifespan variation contributed to 25-30% genetically is mostly increased with age [37-40]. Moreover, this seems to be determined by small effects of many genes [39]. The identification of linkage regions, genes, and pathways that regulate human lifespan has aimed by genomic research performed by genetic, transcriptomic, and epigenomic approaches.

The most interesting pathways identified using animal models are the growth hormone (GH)/insulin/insulin-like growth factor 1 (IGF-1) signaling and mammalian target of rapamycin (mTOR) signaling pathways [37]. The analysis of genetic diversity using genotyping of single nucleotide polymorphisms-SNPs among centenarians and the other population individuals is exerted to detect longevity associated candidate genes, apolipoprotein genes (APOE) Apolipoprotein and transcription factor FOXO3A Forkhead [37]. The most convincing longevity associated genes in human candidate gene studies were performed in cross-sectional designs [37]. Several other genetic approaches, large meta-GWAS, CNV, linkage and next-generation sequencing studies have been applied to identify other loci namely MINPP1 [39], OTOL1 and CAMKIV [39], and potential regions showed suggestive association with longevity. These candidate gene studies demonstrated a role for genes involved in signaling and regulative pathways [40].

Skin Ageing is a multifactorial and complex process driven by both intrinsic and extrinsic factors, including ultraviolet exposure and loss of structure in the extracellular matrix, telomere shortening, and the involvement of sirtuins respectively [41], which is influenced with the probable involvement of heritable and various environmental factors. Several theories have been conducted regarding the pathomechanisms of ageing including cellular senescence and decreased proliferative ability, reduction of cellular DNA repair capacity, loss of telomeres with advancing age, point mutations of extranuclear mtDNA, which may be associated with increased oxidative stress and increased frequency of chromosomal abnormalities [42]. Mechanisms and pathways affected on skin ageing included matrix production, barrier, lipid synthesis, antioxidant capacity and hyperpigmentation are identified by genomics and transcriptomics methods [43].

Two valuable technologies, DNA microarrays and RNA sequencing, are used to transcriptome analysis and to understand genomics and pathways, which are involved in skin ageing and extension of lifespan. A recent microarray study to detect skin ageing related genes

expression showed 1672 genes that were differentially expressed with age; some of these identified skin genes were common to several tissues such as adipose and brain involved to the Wnt, Notch and p53 pathway like CDKN1A encoding p21WAF1, TPP1 and TP53AIP1. Makrantonak et al. provided biomarkers of endogenous human skin ageing in both genders, accentuated the role of Wnt signaling and shows some age-related processes like the decrease in collagens [44].

Despite these advances, fundamental mechanisms of human ageing still remain poorly understood. This may be due to collection of human's internal organs specimens for experimental research purposes that are associated with major practical and ethical obstacles. Alternatively, the use of skin as a common research tool may offer a promising approach. Furthermore, results suggest that skin is a good alternative to understand ageing of different tissues such as CNS [45].

Understanding the impact of genetics and mechanisms of ageing in both human gender and different populations can develop effective strategies to prevent the age-related diseases and improve the healthy lifespan through the development of therapeutic products [46].

Regulation of genes in human skin aging

The main function of the skin is to encompass and protect the body from environmental challenges and to be a sensory indicator of the surrounding world. The epidermis, which is dominated by keratinocytes, forms the skin barrier that protects the body against water loss and external physical, chemical, and biological insults. The transcriptome analysis shows that 63% of all human proteins (n=19692) are expressed in the skin and 412 of these genes show an elevated expression in skin compared to other tissue types (Figure 1) [47]. An analysis of corresponding proteins with regard to tissue distribution shows that most of these proteins are related to squamous differentiation and formation of the outermost cornified layer and expressed in different layers of the epidermis. Additional proteins elevated in skin are expressed in melanocytes, hair follicles and dermal cells with functions including pigmentation, hair development, and connective tissue structure.

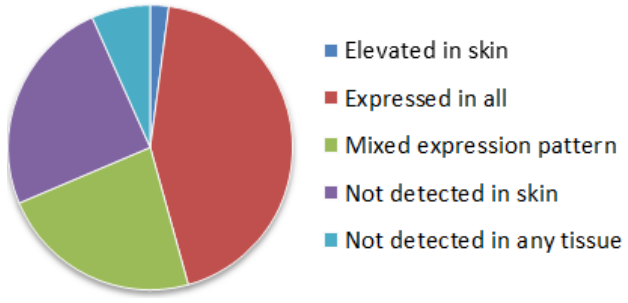

Figure 1: The distribution of all genes across the five categories based on transcript abundance in skin as well as in all other tissues.

Additional proteins elevated in skin are expressed in melanocytes, hair follicles and dermal cells with functions including pigmentation, hair development, and connective tissue structure. Among all the genes related to aging, Collagens, Fibulins and 100 Calcium binding proteins are the most common (Figure 2) [47].

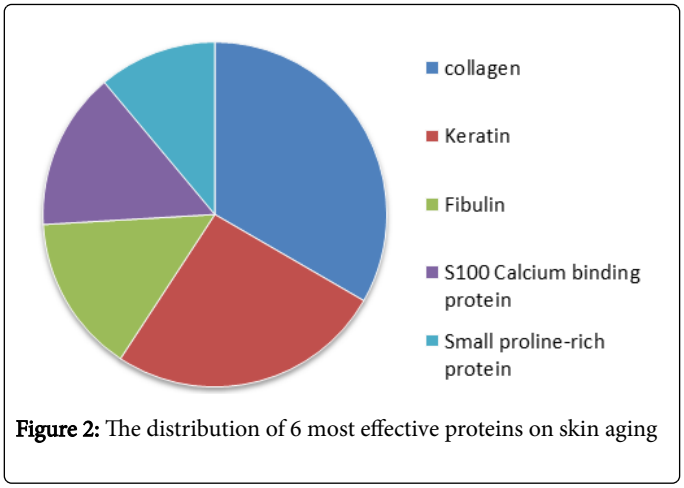

Figure 2: The distribution of 6 most effective proteins on skin aging

Collagen

Collagen is a long-chain amino acid and the most abundant protein in the body. It is composed of the individual amino acids Glycine, Proline, Hydroxyproline, and Arginine. In nature, collagen is found exclusively in animal tissue, especially bones and connective tissue. It is responsible for giving skin elasticity, hair strength, and connective tissue its ability (the ability) to hold everything in place. In fact, the collagen protein makes up 30% of the total protein in the body, and 70% of the protein in the skin [48]. The body's natural collagen production declines with age, and many modern lifestyle factors (like stress, poor diet, gut health imbalances, etc.) can also decrease the body's ability to make it (Figure 3).

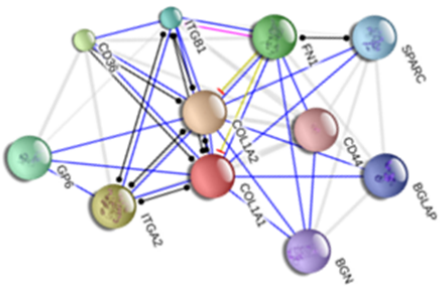

Figure 3: Collagen genes interactions and network.

Collagen is one of the most abundant proteins in the body, and it makes up a large part of our skin, hair and nails. Technically a polypeptide, collagen contains a mixture of amino acids such as proline and glycine, which are found in all connective tissues within the body (Table 1) [48]. While beauty treatments and shampoos trumpet the benefits of collagen on their labels, the real benefits come internally, not from a topical treatment (Figure 4).

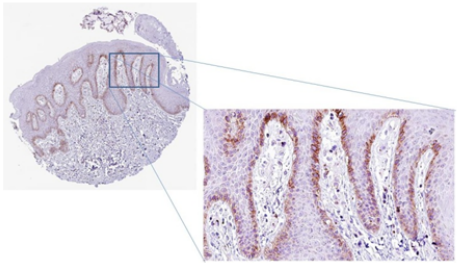

Figure 4: The basal layer contains epidermal stem cells and is the location for proliferation and renewal of keratinocytes. In addition to keratinocytes, melanocytes are also present in the basal layer. Proteins expressed in the basal layer include COL17A1 and TP73.

Name of Gene	Description	Status in Skin Aging
COL1A1	Collagen, type I, alpha 1	UP
COL27A1	Collagen, type 27, alpha 1	UP
COL6A2	Collagen, type VI, alpha 2	UP
COL6A3	Collagen, type VI, alpha 3	UP
COL1A1	Collagen type 1, alpha 1	DOWN
COL1A2	Collagen, type I, alpha 2	DOWN
COL3A1	Collagen, type III, alpha 1	DOWN
COL5A1	Collagen, type V, alpha 1	DOWN
COL5A2	Collagen, type V, alpha 2	DOWN

Table 1: Collagen based Genes related to Skin Aging.

Keratin

Keratin is a protein inside cells. It exists in many types of cells but it is very important for epithelial cells, which make up the skin. Keratin is a type of filament protein, called an intermediate filament. These proteins form long strands inside the cell, hence the name filament. The filaments anchor the cells to each other, which prevents the cells from pulling apart (Figure 5) [49].

Keratin has two main functions in the skin:

1. To hold skin cells together to form a barrier

2. To form the outermost layer of our skin, that protects us from the environment. To form a barrier, epithelial cells anchor together through proteins called desmosomes. Two epithelial cells line up next to each other and attach using desmosomes. The desmosomes act like glue holding the two cells together. Inside the cell are the keratin fibers, holding the desmosomes to the cell. Without the keratin fibers, the desmosomes would just pull the membrane of the cell away from the center (Figure 6).

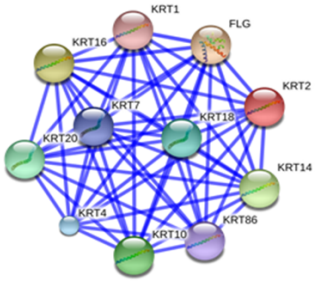

Figure 5: Keratin genes interactions and network.

The keratin anchors the desmosomes to the cell and the desmosomes anchor the cells to each other. The cells attach to each other, and the long filaments within the junction are keratin proteins [50].

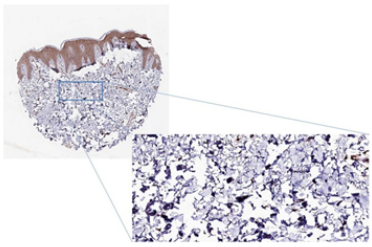

Figure 6: Epidermis-specific type I keratin that plays a key role in skin. Acts as a regulator of innate immunity in response to skin barrier breach: required for some inflammatory checkpoint for the skin barrier maintenance.

The second function of keratin is to form the outer layer of the skin. This happens through keratinocytes in a process called cornification (Table 2). The keratinocytes in the middle of the epithelium starts to make more and more keratin [50].

Name of Gene	Description	Status in Skin Aging
KRT16	Keratin 16	DOWN
KRT17	Keratin 17	DOWN
KRT2A	Keratin 2A	DOWN
KRT6B	Keratin 6B	DOWN
KRT6C	Keratin 6C	DOWN
KRT16	Keratin 16	UP
KRT6A	Keratin 6A	UP

Table 2: Keratin based genes related to skin aging

Fibulin

Fibulins are a multigene family, currently with seven members. Fibulin-1 is a calcium-binding glycoprotein. In vertebrates, fibulin-1 is

found in blood and extracellular matrix. In the extracellular matrix, fibulin-1 associates with basement membranes and elastic fibers (Figure 7). The association with these matrix structures is mediated by its ability to interact with numerous extracellular matrix constituents including fibronectin, proteoglycans, laminins and tropoelastin [51].

Figure 7: Fibulin genes interactions and network.

In blood, fibulin-1 binds to fibrinogen and incorporates into clots. Fibulins are secreted glycoproteins that become incorporated into a fibrillar extracellular matrix when expressed by cultured cells or added exogenously to cell monolayers (Figure 8). The five known members of the family share an elongated structure and many calcium-binding sites, owing to the presence of tandem arrays of epidermal growth factor-like domains (Table 3). They have overlapping binding sites for several basement-membrane proteins, tropoelastin, fibrillin, fibronectin and proteoglycans, and they participate in diverse supramolecular structures [52].

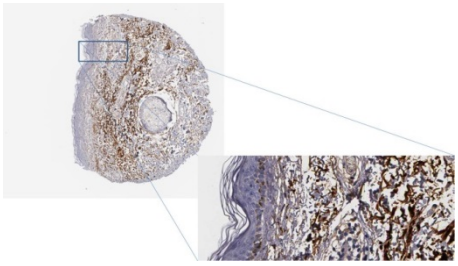

Figure 8: Fibulin-5 was recently found as a secreted extracellular matrix protein that functions as a scaffold for elastic fibers.

Name of Gene	Description	Status in Skin Aging
FBLN1	Fibulin 1	UP
FBLN2	Fibulin 2	UP
FBLN5	Fibulin 5	UP

Table 3: Fibulin based genes related to skin aging

S100 calcium binding protein

The protein encoded by this gene is a member of the S100 family of proteins containing 2 EF-hand calcium-binding motifs. S100 proteins are localized in the cytoplasm and/or nucleus of a wide range of cells, and involved in the regulation of a number of cellular processes such as cell cycle progression and differentiation. S100 genes include at least 13 members, which are located as a cluster on chromosome 1q21 [53]. This protein is widely expressed in various types of tissues with a high expression level in thyroid gland. In smooth muscle cells, this protein co-expresses with other family members in the nucleus and in stress fibers, suggesting diverse functions in signal transduction. Multiple alternatively spliced transcript variants encoding the same protein have been found for this gene (Table 4 and Figure 9) [54].

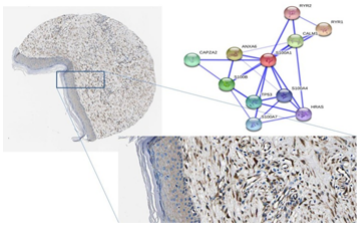

Figure 9: S100 calcium binding A8.

Name of Gene	Description	Status in Skin Aging
S100A2	S100 Calcium binding protein A2	UP
S100A7	S100 Calcium binding protein A7	UP
S100A8	S100 Calcium binding protein A8	UP
S100A9	S100 Calcium binding protein A9	UP

Table 4: Calcium binding protein based genes related to skin aging.

Skin transcriptome

An analysis of the expression levels of each gene made it possible to calculate the relative mRNA pool for each of the categories. The analysis shows that 83% of the mRNA molecules derived from skin corresponds to housekeeping genes, and only 12% of the mRNA pool corresponds to genes categorized as skin enriched, group enriched or skin enhanced. Thus, most of the transcriptional activity in the skin is related to proteins with presumed housekeeping functions as they are found in all tissues and cells analyzed [55].

Gene ontology-based analysis of all the genes defined as skin enriched (n=95), and group enriched with esophagus (n=33) indicate a clear overrepresentation of proteins associated with keratinization, epidermis development, epithelial development, epidermal cell differentiation, and keratinocyte differentiation. Gene ontology terms that are specifically found in skin and not esophagus are genes related to establishment of skin barrier, regulation of water loss, and the ones related to melanin biosynthesis [56].

Ageing proteomics

Biological aging refers to the irreversible process that accumulates changes in vital organs that lead to loss of function or cell death. Although some avoidance have been shown to be partially in contact with aging disease in the senescent organism that is influenced by

genetic, epigenetic and environmental factors, the causes of aging are unknown entirely [57].

As aging is a process in which all of the biological system is involved, we can find the leads causing aging diseases or disorder in changing the relative level of protein expression, post translational modification or protein folding [57-59].

Proteomics approaches aim at studying these features. Proteomics analyzes all of organism's proteins data (proteome). Proteomics technology led to the discovery and identification of proteins that play a fundamental role in cellular aging. The identification of factors involved in this process such as aging related proteins and methods of controlling them can open a way to solve many clinical issues that finally lead to delaying the aging process. In this type of studies, mostly live cells with variety in age, from youth to old, are selected from different tissues and then the completely derived proteins are studied. Also in this section, we will follow the pattern of protein and determine the level of expression using bioinformatics application. Finally, abundance aging associated proteins, the intensity of expression, changing in their three-dimensional structure during the folding and their effects on aging will be recognized.

One of the molecular mechanisms identified in ageing is the loss of proteostasis. Proteostasis or protein homeostasis refers to maintaining proteome balance in the living organisms within individual cells, tissues, and organs that influence the fate of a protein from synthesis and fold to degradation. Protein homeostatic processes are responses to stabilizing proteins. Molecular chaperones carry out these beneficial functions. Chaperones are the group of unrelated protein families that assist synthesized polypeptides to achieve the correct folding and stabilize unfolded proteins by refolding. Heat shock proteins (HSP) as a major group of these chaperons are expressed when induced by environmental heat stress or oxidative stress. It has also been found, HSP levels have decreased in aging. HSP were induced by the activation of heat shock transcription factor (HSF), and then repair damaged proteins. In addition, younger cells are able to recover from low levels of oxidatively damaged proteins by refolding misfolded proteins. If chaperons were unsuccessful to change misfolded protein to correct-folded protein, proteasomal system for degradation of misfolded proteins comes into the game [60].

As shown in model organisms such as Caenorhabditis elegans and Drosophila misfolded proteins can induce other folded proteins to misfolded ones, and they tend to stick together to establish aggregation formation of proteins. Protein misfolding and aggregation have been shown to be associated with aging diseases. Zhang et al. demonstrated that aggregation of α-synuclein protein can cause neurodegeneration by activation of nigral microglia in Parkinson' disease. In the Alzheimer's disease, Cummings et al. detected abnormal accumulation amyloid precursor protein-immunopositive within neurons or neurites. This granular deposition presents as plaques beginning to grow and eventually rupture, then amyloid precursor protein accumulation transport in extracellular space. Subsequent process happens by astrocytes or microglia. For Huntington's disease has been shown huntingtin protein that was encoded by a mutant CAG/polyglutamine gene, was aggregated in patients' brains for all of these diseases. Recent evidence suggests that Type 2 diabetes as a protein misfolding disease occurred by depositing of aggregates of the islet amyloid polypeptide (IAPP) in the endocrine pancreas cells.

Post-synthetic changes in protein composition occur due to external stresses like reactive oxygen species (ROS), Reactive nitrogen species (RNS) or inherent instability of proteins. By increasing reactive oxygen species (ROS) during aging, proteins are changed. ROS attack protein molecules and lead to accumulation of non-enzymatic modifications on them which increase protein carbonyl content by oxidation on arginine, lysine, threonine and proline residues [61]. The most common antioxidant includes vitamins C and E, and the enzymes superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase has been shown to be participated on suppressing of ROS generation. In the aging disease it has been determined a correlation between decline in cellular antioxidants content like glutathione and reduction of life span. The increasing in level of oxidatively modified proteins occur either the accumulation of this altered protein and decreasing proteolysis that scavenging these altered protein. This is the most possible factor responsible for the functional deterioration in aged cells [62].

It seems during aging, chaperones cannot keep up with the rate of protein folding because of the decrease of chaperons' expression and decrease of degradation of aggregation in proteasomal system. On the other hand as we age, our cells encounter all kinds of damage like oxidation. Damage accumulated while responding to environment and decline in cellular antioxidants content. Cells under all of these conditions go toward aging [63].

Components

Antioxidants

Nowadays, the application of natural antioxidants has been considered as an important issue for human health. Increasing of reactive oxygen can be balanced by the production of antioxidant enzymes in the cell, such as catalase, superoxide dismutase (SOD), and glutathione peroxidase. When a cell comes under stress, this balance is interrupted, and the reactive oxygen species can overwhelm the cells and lead to a change in normal cellular behaviors. Oxidative stress can be generated by a variety of stresses such as extreme temperature, and high UV radiation. Many of such stresses can lead to various skin disorders. Therefore, the use of natural antioxidants can help the researchers to find the solution to solve these problems. Among skin antioxidant agents, Resveratrol and Curcumin have been considered as the best choices [64].

High antioxidant activity of Resveratrol against oxidative stress makes it a critical factor in a variety of cutaneous conditions such as skin cancers. Resveratrol has different activities such as anti-proliferative; it also has cellular effects on skeletal muscle formation. It is able to control the cell accumulation via controlling the G1-phase using different mechanisms as well. Resveratrol can suppresses tumor necrosis factor-a, interluekin-17. Furthermore, curcuminoids and Resveratrol have been considered as anti-alzheimer agents [65].

Curcumin is the most important compound of the spice turmeric and is derived from the rhizome of the East Indian plant Curcuma longa. Curumin is also considered as a potent radical scavenger. Curcumin is capable of diminishing the effect of anti-oxidative enzymes such as SOD, CAT, etc. It also has anti-inflammatory, antioxidant, neurotrophic, and antidepressive effects. The new findings suggest the role of curcumin for prostate cancer prevention. Furthermore, curcumin increases the sirtuin level but does not postpone the senescence of human cells production. Finally, curcumin counteract the pro-inflammatory state which can participate in various age-related diseases. In fact, curcumin might directly influence ROS

scavenging and some signaling pathways, which can suppress the pro-inflammatory state involved in the etiology of ageing and age-related diseases [66].

Conclusion

Personalized medicine

The concept of personalized medicine dates back many hundreds of years. It was not until the 19th century, however, that developments in chemistry, histochemistry and microscopy allowed scientists to begin to understand the underlying causes of disease. From here, major advancements in science and technology have allowed healthcare decisions to become increasingly granular over time. With the growth of the pharmaceutical and medical device industries in the 20th century came the rise of genetics, imaging, and data mining. Midway through the century, observations of individual differences in response to drugs gave rise to a body of research focused on identifying key enzymes that play a role in variation in drug metabolism and response and that served as the foundation for pharmacogenetics. More recently, sequencing of the human genome at the turn of the 21st century set in motion the transformation of personalized medicine from an idea to a practice. Rapid developments in genomics, together with advances in a number of other areas, such as computational biology, medical imaging, and regenerative medicine, are creating the possibility for scientists to develop tools to truly personalize diagnosis and treatment [67].

The goal of personalized medicine is to streamline clinical decision making by distinguishing in advance those patients most likely to benefit from a given treatment from those who will incur cost and suffer side effects without gaining benefit [68].

Application

The term "personalized medicine" is often described as providing "the right patient with the right drug at the right dose at the right time. More broadly, "personalized medicine" may be thought of as the tailoring of medical treatment to the individual characteristics, needs and preferences of a patient during all stages of care, including prevention, diagnosis, treatment and follow-up [69].

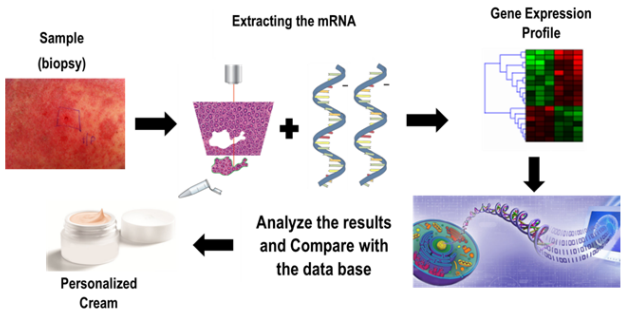

Figure 10: The process to get to the personalized cream.

In order to make personalized cream, by getting biopsy from patients, we extract their mRNA. By using the Microarray technology, we get to the gene expression profile of patient. At this stage we can realize which gene needs to be regulated (up regulate or down regulate). Then according to our data base, we can select the antioxidant which regulate those specific genes (which need to be regulated) and make the personalized cream (Figure 10) [70].

References

1. Rose MR (1994) The Evolutionary Biology of Aging. Oxford Univ Press; Oxford.
2. Campisi J (2013) Aging, cellular senescence, and cancer. Annu Rev Physiol 75: 685-705.
3. Chen QM, Prowse KR, Tu VC, Purdom S, Linskens MH, et al. (2001) Uncoupling the senescent phenotype from telomere shortening in hydrogen peroxide-treated fibroblasts. Exp Cell Res 265: 294-303.
4. Fisher GJ, Kang S, Varani J, Bata-Csorgo Z, Wan Y, et al. (2002) Mechanisms of photoaging and chronological skin aging. Arch Dermatol 138: 1462-1470.
5. Makrantonaki E, Zouboulis CC (2007) Characteristics and pathomechanisms of endogenously aged skin. Dermatology 214: 352-360.
6. Chung JH, Kang S, Varani J, J Lin, GJ Fisher, et al. (2000) Decreased extracellular-signal-regulated kinase and increased stress-activated MAP kinase activities in aged human skin in vivo. J Invest Dermatol 115: 177–182.
7. Jiang F, Zhang Y, Dusting GJ (2011) NADPH oxidasemediated redox signaling: roles in cellular stress response, stress tolerance, and tissue repair. Pharmacol Rev 63: 218–242.
8. Hayflick L (1965) The limited in vitro lifetime of human diploid cell strains. Exp Cell Res 37: 614-636.
9. Lambeth JD (2004) NOX enzymes and the biology of reactive oxygen. Nat Rev Immuno l 4: 181-189.
10. Shenoy NG, Gleich GJ, Thomas LL (2003) Eosinophil major basic protein stimulates neutrophil superoxide production by a class IA phosphoinositide 3-kinase and protein kinase C-??- dependent pathway. J Immunol 171: 3734-3741.
11. Bae YS, Sung JY, Kim OS, Kim YJ, Hur KC, et al. (2000) Platelet-derived growth factor-induced H(2)O(2) production requires the activation of phosphatidylinositol 3-kinase. J Biol Chem 275: 10527-10531.
12. Dang PMC, Fontayne A, Hakim J, Benna JE, Perianin A, et al. (2001) Protein kinase C ´?? phosphorylates a subset of selective sites of the NADPH oxidase component p47phox and Oxidative Medicine and Cellular Longevity 9 participates in formyl peptide-mediated neutrophil respiratory burst. J Immunol 166: 1206-1213.
13. Haas-Kogan D, Shalev N, Wong M, Mills G, Yount G, et al. (1998) Protein kinase B (PKB/Akt) activity is elevated in glioblastoma cells due to mutation of the tumor suppressor PTEN/MMAC. Curr Biol 8: 1195-1198.
14. Maehama T, Dixon JE (1998) The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. J Biol Chem 273: 13375-13378.
15. Ramachandran S, Rajendra Prasad N, Karthikeyan S (2010) Sesamol inhibits UVB-induced ROS generation and subsequent oxidative damage in cultured human skin dermal fibroblasts. Arch Dermatol Res 302: 733-744.
16. Tarpey MM, Fridovich I (2001) Methods of detection of vascular reactive species: nitric oxide, superoxide, hydrogen peroxide, and peroxynitrite. Circ Res 89: 224-236.
17. Niswender KD, Gallis B, Blevins JE, Corson MA, Schwartz MW, et al. (2003) Immuno cytochemical detection of phosphatidylinositol 3-kinase activation by insulin and leptin. J Histochem Cytochem 51: 275-283.
18. Myers MP, Pass I, Batty IH, Van der KJ, Stolarov JP, et al. (1998) The lipid phosphatase activity of PTEN is critical for its tumor supressor function. Proc Natl Acad Sci U S A 95: 13513–13518.
19. Kurose K, Zhou XP, Araki T, Cannistra SA, Maher ER, et al. (2001) Frequent loss of PTEN expression is linked to elevated phosphorylated Akt levels, but not associated with p27 and cyclin D1 expression, in primary epithelial ovarian carcinomas. Am J Pathol 158: 2097-2106.

20. Kohl E, Steinbauer J, Landthaler M, Szeimies RM (2011) Skin ageing. J Eur Acad Dermatol Venereol 25: 873-884.
21. Jenkins G (2002) Molecular mechanisms of skin ageing. Mech Ageing Dev 123: 801-810.
22. Hütter E, Unterluggauer H, Uberall F, Schramek H, Jansen-Dürr P, et al. (2002) Replicative senescence of human fibroblasts: the role of Ras-dependent signaling and oxidative stress. Exp Gerontol 37: 1165-1174.
23. Kang HT, Lee HI, Hwang ES (2006) Nicotinamide extends replicative lifespan of human cells. Aging Cell 5: 423-436.
24. Chen Q, Fischer A, Reagan JD, Yan LJ, Ames BN, et al. (1995) Oxidative DNA damage and senescence of human diploid fibroblast cells. Proc Natl Acad Sci U S A 92: 4337-4341.
25. Zhang GY, Wu LC, Dai T, Chen SY, Wang AY, et al. (2014) NADPH oxidase-2 is a key regulator of human dermal fibroblasts: a potential therapeutic strategy for the treatment of skin fibrosis. Exp Dermatol 23: 639-644.
26. Babior BM (1999) NADPH oxidase: an update. Blood 93: 1464-1476.
27. Ono Y, Fujii T, Ogita K, Kikkawa U, Igarashi K, et al. (1989) Protein kinase C Zeta subspecies from rat brain: its structure, expression, and properties. Proc Natl Acad Sci U S A 86: 3099-3103.
28. Hirai T, Chida K (2003) Protein kinase Czeta (PKCzeta): activation mechanisms and cellular functions. J Biochem 133: 1-7.
29. Rose MR (1991) The Evolutionary Biology of Aging. Oxford, UK: Oxford Univ Press, USA.
30. Kuhle BX (2007) An evolutionary perspective on the origin and ontogeny of menopause. Maturitas 57: 329-337.
31. (2009) Alliance Aging Res. The Silver Book. Chronic Disease and Medical Innovation in an Aging Nation.
32. Natl Cent Health Stat Health, United States (2007) Hayattsville, MD: US Gov.
33. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144: 646-674.
34. Chen CY, Tang C, Wang HF, Chen CM, Zhang X, et al. (2016) Oxygen Reduction Reaction on Graphene in an Electro-Fenton System: In Situ Generation of H2 O2 for the Oxidation of Organic Compounds. ChemSusChem 9: 1194-1199.
35. Balducci L, Ershler WB (2005) Cancer and ageing: a nexus at several levels. Nat Rev Cancer 5: 655-662.
36. Jemal A, Siegel R, Xu J, Ward E (2010) Cancer statistics, 2010. CA Cancer J Clin 60: 277-300.
37. Campisi J, d'Adda di Fagagna F (2007) Cellular senescence: when bad things happen to good cells. Nat Rev Mol Cell Biol 8: 729-740.
38. Sager R (1991) Senescence as a mode of tumor suppression. Environ Health Perspect 93: 59-62.
39. Beauséjour CM, Krtolica A, Galimi F, Narita M, Lowe SW, et al. (2003) Reversal of human cellular senescence: roles of the p53 and p16 pathways. EMBO J 22: 4212-4222.
40. Hayflick L (1965) The limited in vitro lifetime of human diploid cell strains. Exp Cell Res 37: 614-36.
41. Hayflick L, Moorhead PS (1961) The serial cultivation of human diploid cell strains. Exp Cell Res 25: 585-621.
42. Levy MZ, Allsopp RC, Futcher AB, Greider CW, Harley CB, et al. (1992) Telomere end-replication problem and cell aging. J Mol Biol 225: 951-960.
43. Allsopp RC, Chang E, Kashefi-Aazam M, Rogaev EI, Piatyszek MA, et al. (1995) Telomere shortening is associated with cell division in vitro and in vivo. Exp Cell Res 220: 194-200.
44. Collins K (2000) Mammalian telomeres and telomerase. Curr Opin Cell Biol 12: 378-383.
45. McEachern MJ, Krauskopf A, Blackburn EH (2000) Telomeres and their control. Annu Rev Genet 34: 331-358.
46. Weng NP, Hodes RJ (2000) The role of telomerase expression and telomere length maintenance in human and mouse. J Clin Immunol 20: 257-267.
47. Wright WE, Shay JW (2000) Telomere dynamics in cancer progression and prevention: fundamental differences in human and mouse telomere biology. Nat Med 6: 849-851.
48. Zeng X, Rao MS (2007) Human embryonic stem cells: long term stability, absence of senescence and a potential cell source for neural replacement. Neuroscience 145: 1348-1358.
49. Blackburn EH (1991) Structure and function of telomeres. Nature 350: 569-573.
50. Rodier F, Kim SH, Nijjar T, Yaswen P, Campisi J (2005) Cancer and aging: the importance of telomeres in genome maintenance. Int J Biochem Cell Biol 37: 977-990.
51. d'Adda di Fagagna F, Reaper PM, Clay-Farrace L, Fiegler H, Carr P, et al. (2003) A DNA damage checkpoint response in telomere-initiated senescence. Nature 426: 194-198.
52. Takai H, Smogorzewska A, de Lange T (2003) DNA damage foci at dysfunctional telomeres. Curr Biol 13: 1549-1556.
53. Fumagalli M, Rossiello F, Clerici M, Barozzi S, Cittaro D, et al. (2012) Telomeric DNA damage is irreparable and causes persistent DNA-damage-response activation. Nat Cell Biol 14: 355-365.
54. Carneiro T, Khair L, Reis CC, Borges V, Moser BA, et al. (2010) Telomeres avoid end detection by severing the checkpoint signal transduction pathway. Nature 467: 228-232.
55. von Zglinicki T, Saretzki G, Ladhoff J, d'Adda di Fagagna F, Jackson SP (2005) Human cell senescence as a DNA damage response. Mech Ageing Dev 126: 111-117.
56. Nakamura AJ, Chiang YJ, Hathcock KS, Horikawa I, Sedelnikova OA, et al. (2008) Both telomeric and non-telomeric DNA damage are determinants of mammalian cellular senescence. Epigenetics Chromatin 1: 6.
57. Robles SJ, Adami GR (1998) Agents that cause DNA double strand breaks lead to p16INK4a enrichment and the premature senescence of normal fibroblasts. Oncogene 16: 1113-1123.
58. Sedelnikova OA, Horikawa I, Zimonjic DB, Popescu NC, Bonner WM, et al. (2004) Senescing human cells and ageing mice accumulate DNA lesions with unrepairable double-strand breaks. Nat Cell Biol 6: 168-170.
59. Wang C, Jurk D, Maddick M, Nelson G, Martin-Ruiz C, et al. (2009) DNA damage response and cellular senescence in tissues of aging mice. Aging Cell 8: 311-323.
60. Chang BD, Swift ME, Shen M, Fang J, Broude EV, et al. (2002) Molecular determinants of terminal growth arrest induced in tumor cells by a chemotherapeutic agent. Proc Natl Acad Sci U S A 99: 389-394.
61. Coppe JP, Patil CK, Rodier F, Sun Y, Munoz D, et al. (2008) Senescence-associated secretory phenotypes reveal cell non-autonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol 6: 2853-2868.
62. Novakova Z, Hubackova S, Kosar M, Janderova-Rossmeislova L, Dobrovolna J, et al. (2010) Cytokine expression and signaling in drug-induced cellular senescence. Oncogene 29: 273-284.
63. Schmitt CA, Fridman JS, Yang M, Lee S, Baranov E, et al. (2002) A senescence program controlled by p53 and p16INK4a contributes to the outcome of cancer therapy. Cell 109: 335-346.
64. Barascu A, Le Chalony C, Pennarun G, Genet D, Imam N, et al. (2012) Oxidative stress induces an ATM-independent senescence pathway through p38 MAPK-mediated lamin B1 accumulation. EMBO J 31: 1080-1094.
65. Chen QM, Prowse KR, Tu VC, Purdom S, Linskens MH (2001) Uncoupling the senescent phenotype from telomere shortening in hydrogen peroxide-treated fibroblasts. Exp Cell Res 265: 294-303.
66. Nogueira V, Park Y, Chen CC, Xu PZ, Chen ML, et al. (2008) Akt determines replicative senescence and oxidative or oncogenic premature senescence and sensitizes cells to oxidative apoptosis. Cancer Cell14: 458-470.
67. Parrinello S, Samper E, Krtolica A, Goldstein J, Melov S, et al. (2003) Oxygen sensitivity severely limits the replicative lifespan of murine fibroblasts. Nat Cell Biol 5: 741-747.

68. Sedelnikova OA, Redon CE, Dickey JS, Nakamura AJ, Georgakilas AG, et al. (2010) Role of oxidatively induced DNA lesions in human pathogenesis. Mutat Res 704: 152-159.

69. Von Zglinicki T (2002) Oxidative stress shortens telomeres. Trends Biochem Sci 27: 339-344.

70. Di Leonardo A, Linke SP, Clarkin K, Wahl GM (1994) DNA damage triggers a prolonged p53-dependent G1 arrest and long-term induction of Cip1 in normal human fibroblasts. Genes Dev 8: 2540-2551.