MOLECULAR BIOMARKERS OF SKIN AGING AND COSMETIC

Ana Carolina Nogueira Martinhago[A]

[A]Biomedical (2010), specialist in Assisted Human Reproduction (2011), specialist in Aesthetic Biomedicine (2018), Clinical Pathology.

RESUMO

O envelhecimento da pele é um processo natural, causado tanto por fatores intrínsecos ou genéticos, como por fatores extrínsecos. Mundialmente, a demanda por produtos que previnam o aparecimento das características de envelhecimento da pele, tem aumentado acentuadamente. Contudo, é fundamental entender a etiologia do envelhecimento para o desenvolvimento de tratamentos cada vez mais personalizados. O objetivo dessa revisão é discutir como o conhecimento sobre o envelhecimento biológico, os polimorfismos genéticos e as vias metabólicas celulares, podem contribuir na formulação de cosméticos personalizados com ação antienvelhecimento. Estudos em diferentes populações mundiais estão procurando associar polimorfismos de nucleotídeo único (SNPs) com envelhecimento. Pesquisas de SNPs usando a ferramenta de Genome-Wide Association Study (GWAS) mostram resultados heterogêneos, o que dificulta a validação desses biomarcadores. Para superar essas dificuldades, estudos recentes usando a ferramenta Gene Set Enrichment Analysis (GSEA) têm tentado associar modelos biológicos com parâmetros de envelhecimento, o que pode fornecer um conhecimento biológico mais integrado e abrangente. Apesar dos esforços, os marcadores moleculares, com foco dermatológico, ainda não foram validados, sendo necessários estudos em larga escala. Contudo, essas tentativas de avaliação abrangentes dos aspectos genéticos relacionados ao envelhecimento cutâneo em diferentes populações estão permitindo que o setor de cosméticos esteja cada vez mais próximo da ciência, o que beneficia tanto os consumidores quanto as empresas do setor.

Palavras-chave: polimorfismo genético; Polimorfismo de nucleotídeo único; dermatologia

ABSTRACT

Skin aging is a natural process, caused both by intrinsic or genetic factors and by extrinsic factors. Worldwide, the demand for products that prevent the appearance of skin aging characteristics has increased markedly. However, it is essential to understand the etiology of aging for the development of more personalized treatments. The objective of this review is to discuss how knowledge about biological aging, genetic polymorphisms and cellular metabolic pathways can contribute to the formulation of personalized cosmetics with anti-aging action. Studies in different world populations have tried to associate genetic Single Nucleotide Polymorphisms (SNPs) ith aging outcomes. SNPs researchers using Genome-Wide Association Study (GWAS) show heterogeneous results, which makes the validation of these biomarkers difficult. To overcome these difficulties, recent studies

[A]Corresponding author: Ana Carolina Nogueira Martinhago – E-mail: carolina-tn@hotmail.com – ORCID: https://orcid.org/0009-0002-6746-1381

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using Gene Set Enrichment Analysis (GSEA) have attempted to associate biological models with aging outcomes, which may provide a more integrated and comprehensive biological knowledge. Despite efforts, molecular markers, with a dermatological focus, have not yet been validated, requiring large-scale studies. However, these attempts to comprehensively assess the genetic aspects related to skin aging in different populations are allowing the cosmetics sector to be closer to science, which benefits both consumers and companies in the sector.

Key words: genetic polymorphism; Single-Nucleotide Polymorphism; dermatology

INTRODUCTION

Skin aging compared to other organs is a complex process influenced by two main factors: intrinsic, or genetic; and extrinsic, or environmental [1, 2]. Since skin aging suffers from both genetic and environmental influences, the study of these variables is extremely important for precision medicine, in which treatments can be customized according to individual needs [3, 4].

In different global populations, the demand for products that prevent the appearance of skin aging characteristics has increased markedly. However, to offer adequate advice and effective treatment, it is essential to understand the etiology of skin aging, since knowledge about aging and how genetic factors influence this process may allow the development of increasingly personalized anti-aging treatments [5, 6].

The objective of this study is to discuss how knowledge about biological aging, genetic polymorphisms and cellular metabolic pathways can contribute to the formulation of cosmetics with anti-aging action.

MATERIALS AND METHODS

This study consists in a review article with a PubMed database search conducted from 2012 to 2022. The following keywords were used: skin aging; oxidative stress; cosmetics; biomarkers; genetic polymorphisms; Single-Nucleotide Polymorphism (SNP). Only relevant papers were selected.

RESULTS

Genome-Wide Association Studies (GWAS) and Principal Component Analysis (PCA) to identify Single Nucleotide Polymorphisms (SNPs) associated with aging process.

Genetic polymorphisms can be defined as Mendelian traits that exist in a population in at least two phenotypes, neither of which occurs at a frequency less than 1%. Single Nucleotide Polymorphisms (SNPs) are variants in a single base pair in genomic DNA, where different alleles exist in individuals in a given population, occurring at high frequency [7]. Several SNPs can alter the activity of the translated protein, causing alterations in its function. Advances in knowledge about the human genome have revealed a very large number of SNPs for complex traits such as skin aging. However, translating the role of SNPs into clinical practice is still a very complex process [6].

Recently, efforts to identify genetic determinants of skin aging have employed Genome-Wide Association Studies (GWAS). These studies detected significant associations between different outcomes of skin aging with various genomic regions [8, 9].

Thus, heritability studies conducted mainly in European Caucasian twins using GWAS suggest that variations in skin aging characteristics have a genetic component: 55% for facial wrinkles, 41% for pigmented spots and 61% for sagging eyelids [5]. In recent years, several GWAS focusing on skin aging have been published and several genes associated with aging have been identified, some of which have revealed new molecular mechanisms involved in the aging process. These studies focused on various aging outcomes such as perceived facial age [10], facial photoaging [11] and the combined impact of intrinsic and extrinsic factors on facial aging [12]. Other GWAS have been conducted on photoaging-related features such as facial pigment spots [13, 14]. Together, these studies identified genetic variants in several human chromosomes, such as 1, 3, 4, 5, 6, 9, 16, 20, 21 and X [15].

Thereby, the Solute Carrier Family 45 Member 2 (SLC45A2) () gene encodes a protein involved in the production of melanin, through the transport of tyrosinase and/or protons into melanosomes. In German and Japanese populations, SNPs of this gene associated with variations in hair, skin and eye color have been identified [12, 16]. Studies have shown that pigmentation is a critical process of skin aging, but the genetic predisposition has not yet been fully investigated. Thus, Law et al. (2017) [15] performed a meta-analysis involving GWAS of 1,671 twin pairs and 1,745 singletons obtained from three independent cohorts. Thus, it was verified for the first time that the SNP, rs185146, close to the SLC45A2 gene, is associated with skin aging. In another study carried out by Okamura et al. (2019) [17], the 4-bp deletion variant (rs984225803) in the promoter region of SLC45A2 was associated with color variation among a Japanese population.

The study carried out by Law et al. (2017) [15], using BG6, also verified that two previously identified SNPs, rs12203592, close to the IRF4 (Interferon regulatory factor 4) gene and, rs4268748, close to the MC1R (melanocortin-1 receptor) gene, are associated with photoaging and wrinkling. Furthermore, the degree of penetrance for red hair of MCR1 gene alleles, rs1805007 and rs1805008, were associated with skin aging and sunburn. The MCR1 gene is one of those responsible for skin and hair melanogenesis, as well as for sun sensitivity and poor tanning ability, regardless of ethnicity. Some MCR1 polymorphic variants have been linked to a high risk of severe photosensitivity and skin cancer in European

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populations, regardless of age, skin color, presence of wrinkles, lifestyle, and sun exposure. Other studies have shown that MC1R polymorphisms are associated with sunspots, which interfere with perceived age by up to 2 years [10].

In turn, Jacobs et al., (2015) [13] performed a GWAS for pigment spots in 2,844 Dutch individuals. The study identified a significant association between pigment spots and four genetic loci: MC1R (compound heterozygosity score); IRF4 (rs12203592); RALY/ASIP (rs6059655); and BNC2 (rs62543565). The results were successfully replicated in an independent Dutch cohort. Although the four genes were previously associated with variation in skin color and risk of skin cancer, the authors concluded that these genetic variants contribute to the acquired amount of facial pigment spots during aging independently of basal melanin production.

Additionally, Ng & Chew (2022) [3] performed a systematic review of 44 GWAS studies on skin aging and identified 19 promising SNPs. The study found that pleiotropy is a recurring theme among skin aging genes and the SNPs were mainly located on chromosomal band 16q24.3 and were related to skin color. Since numerous genes on chromosomal band 16q24.3 and skin color genes show pleiotropy, this work proposes that the genes traditionally identified as contributors to skin color have functions other than pigmentation and that the contribution of genes located at 16q24.3 should be further investigated.

A study conducted by Le Clerc et al. (2013) [11] using GWAS identified an association between the STXBP5L (syntaxin binding protein 5-like) gene, which is expressed in several tissues, including the skin, with facial photoaging in French women. The authors found an association of the SNP, rs322458, which was in linkage disequilibrium [8] with intronic SNPs of the STXBP5L gene, with the severity of photoaging. On the other hand, the rs322458-AA genotype was inversely linked with the severity of skin aging. The SNP, rs322458, was also associated with wrinkles and sagging, regardless of the degree of photoaging. However, this SNP was not associated with solar lentigines, suggesting that its role in photoaging does not include pigmentary disorders and that molecular mechanisms may be shared by sagging and wrinkling. The study also found another SNP that increases the expression of the FBXO40 (F-box protein 40) gene, rs6775899, in the skin. FBXO40 is a modulator of the IGF1 (insulin-like growth factor 1) gene, which regulates human longevity and length of life in animal models.

Solar lentigines are a common feature of sun-induced skin aging. However, little is understood about the genetic factors that contribute to its development. A GWAS focusing on solar facial lentigines emphasized the possible role of the HLA region in their occurrence. This study points to several mechanisms involved in the severity of facial lentigines, including HLA/immunity and the melanogenesis pathway (Laville et al., 2016). GWAS identified genetic loci associated with solar lentigines on the face in 502 middle-aged French women. Nine SNPs, clustered in two independent blocks on chromosome 6, have been associated with solar lentigines. The first block, in the 6p22 region, corresponded to intergenic SNPs and exhibited a significant association with solar lentigines. The second block, within the HLA 6p21 region, was associated with decreased HLA-C expression. These results indicate the participation of HLA/immunity in the pathogenesis of solar lentigines. This study also confirmed the association of the IRF4 gene with solar lentigines observed by Jacobs et al. (2015) [13].

Furthermore, the study conducted by Laville et al. (2016) [14] also revealed an association between two SNPs (rs62250968 and rs35017084) of the MITF (melanocyte-inducing transcription factor) gene with solar lentigines. The MITF gene encodes a key transcription factor for melanogenesis, and it is involved in differentiation, proliferation, and survival of pigment cells [14].

In turn, Viekorten et al. (2012) [16], in a study with German and Japanese women, associated the SNP rs26722, of the SLC45A2 (Solute Carrier Family 45 Member 2) gene, with the occurrence of lentigines. This study showed that lentigines located on the cheeks, often attributed to skin aging, are more frequent in Japanese women than German women. Moreover, it provides evidence that this ethnic difference might, at least in part, be due to differences in genetic variants that modify melanin synthesis [16].

Changes in the extracellular matrix caused by matrix metalloproteinases (MMPs) may contribute to skin wrinkling, characteristic of premature aging. The MMP1 (matrix metallopeptidase 1) gene encodes collagenase MMP1, which degrades collagen and can lead to the formation of wrinkles. The MMP-1 gene has several genetic variants, including rs1938901, whose T allele is associated with greater expression of the protein, consequently greater production of the MMP1 enzyme, contributing to collagen degradation and wrinkle formation. In addition, when exposed to sunlight, carriers of the T allele may have an 8-fold greater expression of MMP1, which accelerates the photoaging process, contributing to the formation of wrinkles [18].

Another outcome of aging is sagging eyelids. Thus, a GWAS highlighted the possible role of the TG1F1 (TGFB induced factor homeobox 1) gene in eyelid sagging. A meta-analysis of GWAS from 5,578 Dutch individuals and 1,053 twins from United Kingdom showed a significant recessive protective effect of the C allele of rs11876749. This variant is located close to TGIF1, which is a known gene associated with skin aging. In addition, the study identified other risk factors for sagging eyelids, such as: male sex, lighter skin color, high body mass index, and possibly current smoking [5].

A study conducted by Gao et al. (2017) [19] in 502 Chinese women found a significant association between the SNP rs2066853 in exon 10 of the AHR (aryl hydrocarbon receptor) gene and crow's feet. This SNP leads to an amino acid change (Arg554Lys) in AHR gene and has been associated with a higher susceptibility to the effect of environmental exposures to substances such as PAH and dioxin-like chemicals. This is congruent with the findings because crow's feet are part of extrinsic skin aging, and therefore a mainly environmentally induced sign of skin aging. Furthermore, there was an association between SNP rs10733310 in intron 5 of BNC2 (basonuclin 2) and pigmented spots. This is in line with the results of previous studies showing that variants in *BNC2* are associated

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with skin color [20] and the development of facial pigment spots [13]. Additionally, the SNP, rs11979919, located 3 kb downstream of COL1A2 (collagen type I alpha 2 chain), has been associated with eyelid laxity. Mutations in the COL1A2 (collagen type I alpha 2 chain) gene are associated with Ehlers-Danlos syndrome, which includes hyperextensibility of the skin and sagging of the eyelids caused by genetic defects in collagens I and V, which is consistent with the findings [19].

Although the previously cited studies were performed in European and Eastern populations, variants in the MC1R, IRF4 and SLC45A2 genes have also recently been associated with skin aging in Latin American populations [8]. In this study, in 6,254 Latin American individuals, four genome regions associated with aging outcomes were identified. Two were associated with wrinkling (1p13.3 and 21q21.2), one with mole count (1q32.3) and one with wrinkling and mole count (5p13.2). The associated SNPs at 1p13.3 and 5p13.2 are intronic within VAV3 (vav guanine nucleotide exchange factor 3) and SLC45A2, respectively. The SNPs at 1q32.3 are close to the SLC30A1 (solute carrier family 30 member 1) gene, and the SNPs at 21q21.2, occur in a desert gene. Thus, the genes, VAV3 and SLC30A1, were identified as two new candidates impacting on wrinkling and mole count, respectively. The study also corroborated the role of SNPs from the IRF4 and MC1R genes in skin aging.

Studies have also been conducted to identify genes that promote youthful facial skin. After analysis involving replication groups, three SNPs were associated with the youth phenotype: rs6975107, in an intronic region of KCND2 (potassium voltage-gated channel subfamily D member 2); rs318125, downstream of DIAPH2 (diaphanous related formin 2); and rs7616661, downstream of EDEM1 (ER degradation enhancing alpha-mannosidase like protein 1). DIAPH2 has been linked to premature ovarian failure, an aging phenotype in humans. EDEM1 is associated with life expectancy in animal models, although not in humans. KCND2 is expressed in human skin but has not been associated with aging. Thus, this study highlighted new candidate genes to study the molecular basis of healthy skin aging [12].

Principal Component Analysis (PCA) is another approach to studying the genetic and environmental aspects of the aging process. In a recent study conducted by Pardo et al (2020) [21], data from 1,790 individuals were analyzed according to seven features of skin aging. This epidemiology study data identified three main components associated with photoaging: hypertrophic component (global wrinkling; perceived age; Griffiths grading); atrophic component (pigmented spots; telangiectasia); and cancer component (actinic keratosis; keratinocyte cancer). Association analysis showed different effects of environmental and genetic factors on the three components, with genetic variants being more significantly associated with the atrophic component. Thus, the SNP (rs12203592) of the IRF4 gene was significantly associated with pigmented spots, which corroborates the study conducted by Jacobs et al. (2015) [13]. On the other hand, individuals with a predominance of the hypertrophic component may benefit more from the intervention to modify lifestyle factors, while this may be less relevant for individuals with the atrophic component.

In view of these studies, some private companies are using the analysis of various polymorphisms, with the aim of personalizing care in skin aging. Depending on the combination of polymorphisms and the lifestyle questionnaire, a personalized cream formulations recommended to the patient, with the aim of increasing skin hydration and decreasing wrinkle formation. However, many of these results have not yet been published, being seen with great restriction by the scientific community [22].

Identification of metabolic pathways and gene clusters associated with skin aging

Recent studies have verified that individual SNPs identified in GWAS studies do not represent the full impact of genetics on complex polygenic phenotypes such as skin aging. These individual SNP associations identify specific loci with strong influence on the phenotype, but do not provide the biological mechanisms involved in the processes [23].

To overcome these limitations, strategies have been developed that attempt to integrate biological knowledge more comprehensively. One such approach is the analysis of biological pathways associated with a specific phenotype, using Gene Set Enrichment Analysis (GSEA) [24]. In the GSEA, a pathway is represented by a set of genes involved in a biological network. The underlying concept is that multiple genes involved in the same biological pathway may contain genetic variants, each one with a moderate effect that would not be identified using GWAS alone [25].

The identification of metabolic pathways provides more functional insights to understand the molecular mechanisms involved in skin aging and, consequently, will provide more therapeutic or diagnostic targets for specific aspects of this process. This approach leads to a more comprehensive integration of biological mechanisms than the usual approach of SNPs performed by GWAS [23, 26].

In a study carried out by Rahmouni et al. (2022) [23], in 502 French women, 795,063 SNPs were identified, and new associations in biological pathways for four main outcomes of skin aging were also analyzed: photoaging, solar lentigines, wrinkling and sagging. For each outcome, a GWAS and subsequently a GSEA were performed to look for molecular pathway associations.

Thus, the main pathways associated with photoaging were: melanogenesis, nucleotide excision repair and primary immunodeficiency. While solar lentigines were associated with melanogenesis and immune system pathways, wrinkling was associated with nucleotide excision repair, proteasome, and primary immunity. Regarding the sagging phenotype, the main associated pathways were: amino sugar and nucleotide sugar metabolism, nucleotide excision repair, melanogenesis, primary immunodeficiency and mTOR signaling pathway [23].

Thus, it is possible to observe that the outcomes of aging may have specific molecular mechanisms, such as mTOR signaling pathway and proteosome. However, they may share molecular mechanisms. In addition to analyzing biological models individually,

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it is also important to have a global view of these pathways, because skin aging is a complex process involving a combination of cellular and molecular pathways [27, 28].

The work conducted by Rahmouni et al. (2022) [23] is the first study based on analyses of metabolic pathways related to skin aging. The study highlights highly relevant metabolic pathways in photoaging, solar lentigines, wrinkling and sagging, which can be specific and/or shared. However, as with any large-scale study, replication in other cohorts will be needed to confirm these results.

It should be noted that the pathway-based approach is powerful but has some limitations. The understanding of human gene functions is incomplete, and some genes have not yet been characterized. So, the pathways deposited in the database may not be fully representative of all the biological networks. However, the refinement of statistical approaches has helped to overcome these limitations [23, 25].

Another very interesting work, although previous, was carried out by Naval et al. (2014) [29]. In this work, the authors described the frequencies of genetic polymorphisms in 120 Spanish women and distributed them in gene clusters. Based on the contribution of the SNP, 10 clusters related to skin aging were identified. The polymorphisms were related to genes that codify proteins involved in the antioxidant capacity, elasticity, and hydration of the skin, such as NAD(P)H dehydrogenase [quinone] I; matrix metalloproteinase-I, 3 and 9; superoxide dismutase II; nuclear factor erythroid 2-related factor 2; catalase; interleukin-6, aquaporin-3; glutathione peroxidase I.

Different skin care needs depend on the genetic variants present in each of the genetic clusters, which presents a unique combination of needs for each of the three main characteristics studied: antioxidant capacity, elasticity, and hydration of the skin. Thus, it is not only necessary to complement the lack or low activity of certain skin functions, but the excess of active ingredients in cosmetics can also be harmful for those individuals whose genetic heritage already provides strong natural capabilities [29].

DISCUSSION/CONCLUSION

The use of genetic biomarkers for personalized aesthetic treatments is not yet a validated condition, since there is a wide variation in SNPs-type polymorphisms, according to the evaluated population. In addition, there is a lack of information on the identification, frequency and clustering of gene variants associated with events related to skin aging, such as antioxidant capacity, metabolism, elasticity and hydration capacity [29]. Thus, replication across independent datasets is critical for confidence in GWAS findings [14].

A disadvantage of these GWAS-based findings is that most were performed in individuals of European descent. The robustness of these associations still needs to be established, since most associations were observed in single studies, and often these studies examined relatively small samples. On the other hand, there are also several gene loci related to aging outcomes, which were detected in several independent GWAS, and the robustness was established by large meta-analyses comprising thousands of individuals [8]. This fact demonstrates the importance of performing meta-analyses for the reliability of the results.

However, some biomarkers seem to be more promising, such as the polymorphisms of the MCR1, IRF4, SLC45A and NAD(P) H dehydrogenase [quinone] I genes, which have potential for application. Some companies have offered tests based on genetic polymorphisms for the indication of a personalized cosmetic formulation. In its turn, the scientific community views this with restriction, because there is still no specific genetic variant explicitly linked to skin health, so it is unclear what truly applicable information the tests provide [22].

Currently, other approaches have been developed to overcome the limitations imposed by the analysis of SNPs. Among these approaches, GSEA analyzes biological pathways associated with a particular phenotype. Through this approach, aging outcomes have been associated with several metabolic pathways, which may overlap, depending on the evaluated outcome.

Similar to personalized medicine for disease studies, aesthetic medicine has a challenging path, however, very promising. These attempts to evaluate genetic polymorphisms and cellular metabolism pathways, related to skin aging in different populations, are allowing the cosmetics sector to be closer to science, which benefits both consumers and companies in the sector.

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