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Genetic basis for skin youthfulness

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Abstract Aging skin is a consequence of both intrinsic factors, including genetics, and extrinsic factors, including environmental exposures such as ultraviolet (UV) radiation and smoking. This contribution focuses on intrinsic factors that promote aging skin. Specifically, in this contribution we review the literature describing how single nucleotide polymorphisms, epigenetic changes, variable gene expression, microRNA, and mitochondrial depletion relate to skin aging. Investigations studying intrinsic factors associated with skin aging are important as they promote a better understanding of the underlying pathophysiology of aging skin. This contribution also describes potential avenues for future genetic research in skin aging. Molecular mechanisms that may be therapeutically intervened upon are of particular interest given the cultural value placed on youthful appearing skin. Future research efforts will hopefully reveal a means upon which to intercede on the skin aging process.

Introduction

Maintaining youthful-appearing skin is important to many individuals across different cultures, backgrounds, and ages. Humans value younger looking skin and can reliably identify it and likewise associate it with increased attractiveness.[1] Extrinsic factors associated with skin aging are well established and include smoking, ultraviolet (UV) damage, and low body mass index.[2–4] In contrast, more recently, studies have begun to investigate intrinsic factors contributing to skin aging, such as the genetic basis of skin aging. While genes promoting youthfulness and longevity throughout the body have been identified, there are considerably fewer genes specifically linked to dermal longevity.[5–7] Fortunately, advances in technology have fostered an unprecedented increase in our capacity to understand the human genome and its far-reaching effects, including the contribution to skin aging.[8] Elucidation of the underlying mechanisms of skin aging is fundamental to identifying potential therapeutic targets that enable individuals to maintain a youthful appearance. This review summarizes the current understanding of several genetic determinants in skin aging and provides a framework for what future studies may entail.

Single nucleotide polymorphisms associated with skin aging

Several genome-wide association studies (GWAS) have been performed identifying single nucleotide polymorphisms (SNPs) associated with skin aging. GWAS assess numerous SNPs simultaneously to identify SNPs associated with the

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presence of disease or of an observed phenotypic characteristic.[9,10] One gene implicated in skin aging by several GWAS analyses is *MC1R*, a gene involved in the synthesis of melanin via production of melanocortin 1 receptor.[11] Variations in *MC1R* alleles are responsible for pigmentation. Mutations in this gene manipulate the ratio of eumelanin to pheomelanin, influencing the color of hair and skin.[12–14] Interestingly, *MC1R* appears to be protective against precancers and cancers, and loss-of-function mutations in this gene are associated with the development of nonmelanoma skin cancers.[13]

In aging skin, SNPs associated with *MC1R* have also been implicated in both global and specific features of skin aging. In a GWAS study performed in Dutch European patients, of 8 million SNPs studied, the strongest relationship among skin aging was observed for SNPs associated with *MC1R*. Independent of sex, age, skin damage, and skin color, homozygotes for the *MC1R*-risk haplotype appeared, on average, 2 years older compared with those who did not have this haplotype. As the observed results were independent of skin color, the authors suggested that the role *MC1R* plays in skin aging is potentially mediated via inflammation, independent of the role of *MC1R* in melanin production.[11]

A study performed in a cohort of French women also implicated *MC1R* in skin aging. The results demonstrate that certain loss-of-function variants of the *MC1R* gene are associated with increased photoaging risk. Specifically, the alleles *MC1R*D84E*, *MC1R*D294H*, *MC1R*I155T*, *MC1R*R142H*, *MC1R*R151C*, and *MC1R*R160W* conferred the greatest risk for photoaging. Subjects who were carriers for one of these alleles had a nonsignificant trend toward increased risk of photoaging. In individuals who were carriers for two of these alleles, the risk of photoaging was six-fold that of those who carried two wild type alleles. Of these alleles, *MC1R*D84E*, *MC1R*R151C*, and *MC1R*R142H* carried the greatest risk. After controlling for sun exposure and skin color, these polymorphisms were still associated with skin photoaging. The authors also suggested that *MC1R* may contribute to skin aging beyond its effects on melanin synthesis.[11,15] One such mechanism by which allelic variants of *MC1R* may contribute to skin aging is rooted in the role that different melanin compounds play in the balance of reactive oxygen species (ROS). In particular, pheomelanin may promote the production ROS whereas eumelanin may scavenge ROS.[14,15] The authors proposed that an increased ratio of pheomelanin to eumelanin may allow for increased generation of ROS, causing damage to the skin and promoting photoaging.[15]

In a meta-analysis that assessed data from five GWAS, SNPs in and near *MC1R*, *SLC45A2*, and *IRF4* had genome-wide significant associations with skin aging. The Beagley and Gibson (BG6) microtopography scoring system was used in this study to measure skin aging. The method involved examining magnified silicon impressions of skin to assess for topographic changes and then assigning a value on a six-point scoring system to the observed topography, where an increasing score correlated with photoaging.[16,17] As expected, alleles associated with decreased photoaging were those responsible for higher levels of skin pigmentation. For example, *MC1R* alleles associated with red hair and lower levels of pigmentation were associated with higher BG6. Further, among the *MCR1* red hair alleles, alleles with higher penetrance for red hair correlated with increasing BG6 score.[16]

Lastly, an analysis of individuals from the Rotterdam study demonstrated that *MC1R* has significant associations with facial pigmented lesions, a feature of skin aging, defined in this study to include solar lentigines or seborrheic keratoses. The authors also identified additional SNPs in or adjacent to three other genes associated with facial pigmented spots, including *RALY/ASIP* (heterogeneous nuclear ribonucleoprotein, agouti signaling protein), *BNC2* (basonuclin 2), and *IRF4* (interferon regulatory factor 4). These genes, like *MC1R*, are associated with skin color. The authors demonstrated that the genome-wide associations with these four loci identified for skin aging were partially independent of skin color.[18]

For other SNPs identified in GWAS, outside of those associated with genes involved in skin pigmentation, the mechanism by which these SNPs are associated with phenotypic characteristics of skin aging is sometimes less readily apparent. It is important to acknowledge that identification of a SNP through a GWAS analysis does not necessarily indicate a causal relationship between that SNP and the observed phenotypic characteristic with which it is associated. Identified SNPs may simply be a signal for the causal genetic difference responsible for a feature of skin aging and be in linkage disequilibrium with said causal SNP or gene.[10,19]

In a study of Caucasian women of European descent, for example, the SNP rs322458 was found to be significantly associated with global features of skin photoaging. In regard to specific features of skin aging, this SNP was significantly associated with the presence of skin sagging and wrinkles but was not significantly associated with the presence of lentinges. The haplotype map HapMap was used to identify potential relationships; these analyses identified that the SNP rs322458 is in linkage disequilibrium with multiple SNPs in the *STXBP5L* gene. How this relates to skin aging, however, remains unclear. Through exploration of bioinformatics databases, the authors also identified that the rs322458 SNP was in linkage disequilibrium with a SNP that increases expression of FBOX40 in the skin. FBOX40 is involved in myogenesis and inflammation; the authors suggested that these are potential mechanisms which may partially explain the association between the rs322458 SNP and associated characteristics of skin sagging and wrinkling.[20] This SNP was additionally examined in a meta-analysis and found to correlate with skin photoaging in that study. As suggested by the authors, the identification of a SNP across multiple studies with unique cohorts or in studies looking at distinct features of skin aging strengthens the evidence that the SNP is truly a marker of genetic variation that contributes to the characteristic of interest.[16]

Importantly, one limitation in the GWAS literature to date, including the skin aging literature, is that existing

studies have largely been performed in Caucasian populations.[21] Replicating GWAS in individual ethnic populations is important for highlighting genetics signatures unique to different populations.[19] For example, a study demonstrated that SNPs associated with three genes, aryl hydrocarbon receptor (*AHR*), basonuclin 2 (*BNC2*), and collagen type-1 alpha-2 gene (*COL1A2*), are associated with features of aging in a Han Chinese population of 502 women from Taizhou. A SNP in an exon of *AHR* had significant associations with lateral canthal rhytids, otherwise known as "crow's feet."[19] Other studies have identified that this SNP may heighten susceptibility to environmental exposures, potentially promoting DNA damage or cancer.[19,22,23] Therefore, the authors suggested that this SNP may similarly increase susceptibility to environmentally mediated skin aging and promote the development of crow's feet. Additionally, the SNP associated with *BNC2* was found to be associated with pigmented spots on arms, whereas a corresponding minor allele was protective against pigmented spots. As other studies that have identified roles for *BNC2* in skin pigmentation, this provides a potential mechanism for the formation of pigmented spots.[19,24] Upper lip wrinkles were also found to be associated with *BNC2*, although this signal was only minor. Finally, a third SNP located near *COL1A2* was associated with eyelid laxity; the corresponding minor allele had a protective effect against eyelid laxity.[19]

In another approach, studies have identified SNPs associated with younger-appearing skin. In a study of people of Ashkenazi Jewish descent (part of the LonGenity database) in New York, six SNPs were identified that were associated with skin youthfulness. These SNPs were confirmed in two replication cohorts, which revealed that three SNPs were significantly associated with skin youthfulness. These SNPs were either in or near the genes diaphanous homolog 2 (*Drosophila*) (*DIAPH2*), potassium voltage-gated channel, Shal-related family member 2 (*KCND2*), and ER degradation enhancer (*EDEM1*). The relationship of these SNPs to skin youthfulness was not readily clear.[7] In sum, many SNPs have been identified in GWAS studies that are associated with skin aging. Further investigation into the relevance of these SNPs is essential for a more comprehensive understanding of how genetic variation contributes to skin aging.

Epigenetics: DNA methylation and skin aging

The concept of epigenetic drift describes changes in methylation that occur with age across various tissues including the skin.[25–30] One study identified that both age and sun damage correspond to widespread hypomethylation. Further, the degree of hypomethylation observed correlated with the severity of photoaging on clinical exam. Interestingly, these hypomethylated regions corresponded to hypomethylated regions found in squamous cell carcinoma samples and colon cancer.[28]

In contrast, other studies suggest that hypermethylation of the methylome is a more commonly observed feature of skin aging. For example, one study identified a unique pattern of hypermethylation affecting only a small portion, less than 1%, of sites studied.[30] This study, however, has been critiqued by other authors as limited in its methods. For example, the technology used only focused on CpG islands, which are regions of dense CpG dinucleotides.[28] Regional variation in methylation can be appreciated outside of CpG islands, including at both CpG island shores and the "open seas," and using a technology that assesses each of these regions within the methylome is important.[28]

When juxtaposing the methylomes of young and old individuals, another study failed to identify large-scale epigenetic changes; however, the authors did observe localized methylation changes that were smaller, ranging in size between 100 to 150 base pairs. These methylation changes were primarily found at enhancers and promoters, which suggests that localized epigenetic changes associated with skin aging may promote changes in gene expression. The authors also studied the transcriptome for differences in gene expression between young and old samples, identifying 75 differentially expressed genes, including several genes involved in skin homeostasis.[27]

Similarly, a recent study identified that increased homogeneity of methylation and hypermethylation of CpG islands occur in aging skin. Methylomes examined from younger participants were very similar to one another, whereas increased variation of methylation patterns was appreciated in epidermal samples obtained from older participants. Methylomes analyzed from older samples were less clearly delineated, which the authors referred to as "age-related erosion of DNA methylation patterns." This was in contrast to younger methylomes in which the methylation pattern was very distinct.[26]

In sum, a variety of findings have been reported regarding change in the methylome observed with skin aging. This is likely partially a consequence of the different technologies employed by researchers, each with their own unique capacity to identify changes in methylation at varying resolutions. Nonetheless, perhaps the central conclusion to draw from these studies is that epigenetic changes seem to occur in the skin over time and these changes likely have functional consequences in gene expression, which may explain observed phenotypic changes in aged skin.

It remains unclear, however, what molecular processes underlie age-related associated changes in methylation.[25] Proteins responsible for changes in methylation and acetylation are therefore of particular interest, especially given the potential to manipulate these agents as therapeutic targets to mitigate deleterious changes in the methylome that may promote skin aging. Interestingly, knockdown of DNA methyltransferase 1 (DNMT1), an enzyme that maintains DNA methylation, promoted a premature-aging phenotype in a murine model. This observation led researchers to investigate the role on DNMT1 in skin aging in human fibroblasts. Elevated DNMT1 expression was observed in younger fibroblasts compared with passage-aged fibroblasts, in which

DNMT1 expression was diminished. Via bioinformatics, the authors identified a microRNA, miR-377, with homology and capacity to bind the 3′UTR of DNMT1. Expression of this microRNA was elevated in passage-aged fibroblasts, potentially explaining the observed decrease in DNMT1 expression. Similarly, fibroblasts cultured from young and old skin donors demonstrated differential miR-377 and DNMT1 levels; old samples had decreased DNMT1 and elevated miR-337 expression.[31]

Overexpression of miR-377 expression in young fibroblasts promoted cell senescence and decreased fibroblast proliferation, but the converse was observed with inhibition of miR-377 in older fibroblasts. These results suggest that miR-377, via DNMT1, may modulate methylation and expression of genes, such as p53, a tumor suppressor gene which may also play a role in the aging process and contributes to skin fibroblast cell death and skin aging.[31]

Lastly, other studies have intriguingly demonstrated that exposure to UV radiation can modulate DNMT1 expression. Specifically, increased expression of DNMT1 occurs with UV radiation, promoting hypermethylation and decreased expression of tissue inhibitor of metalloproteinase 2 (TIMP2).[32] TIMP2 is part of a larger family of proteins that regulate matrix metalloproteinases and the balance of collagen homeostasis within the skin.[33] UV radiation, therefore, in modulating expression of TIMP2 via epigenetic changes, may promote collagen breakdown contributing to skin aging.[32]

Gene expression

Gene expression in aging is a hot topic for current research, with an increasing number of studies exploring how changes in gene expression relate to extrinsic and intrinsic aging within the epidermis, dermis, and other tissues of the human body. Recent studies have identified numerous genes that contribute to the cellular processes that underpin skin aging. Changes in gene expression can promote and protect against skin aging, which provide many targets for antiaging research and treatment development. Research studies either focus on changes across cohorts in different age categories, changes between sun-exposed and sun-protected skin, or a combination of the two. Previous research examining differentially regulated genes in skin aging found 105 genes that had significantly altered expression—determined by at least a 1.7-fold change in expression—in aged skin, including 43 genes downregulated and 62 upregulated.[34] Gene changes were associated with various mechanisms in the skin, including cell adhesion, apoptosis, extracellular matrix, metabolism and immune response, among others, highlighting the complexity of skin aging on a genetic scale. Major functional categories of gene expression changes included transcription factors, cell cycle control, extracellular matrix, signaling pathways, and cytoskeletal components.

A recent study examined intrinsic and extrinsic factors that contribute to skin aging. This study evaluated molecular changes in photoprotected versus photoexposed skin with increasing age and assessed changes in gene expression in women who appeared younger than their chronologic age. The study involved cohorts separated by decades, from 20 to 24 years old, 30 to 34 years old, and up to 70 to 74 years old in a Caucasian population. One 2-mm punch biopsy was obtained from the preauricular cheek, two 4-mm punch biopsies were taken from the dorsal forearm and buttocks, and a 4-mm punch biopsy was taken from the scalp, representing photoexposed and photoprotected skin. A DNA swab was taken from the oral mucosa. Each participant completed a questionnaire about sun exposure, sunscreen use, and other skin care habits.[35]

Based on genotyping, most participants were of Northern European and British-Irish backgrounds. Using standardized photography, apparent age was associated with chronologic age. Within each decade of subjects there was a range of apparent ages, which was used to identify subjects considered slow agers versus fast agers. On histology, dermal elastosis increased with age in the samples from the face and dorsal forearm, typically beginning in the 40-year-old cohort. In contrast, no increase in dermal elastosis with age in buttocks samples was observed, demonstrating the strong role that UV exposure plays in skin aging.[35]

The results of this study revealed that there are progressive changes that occur in the skin from age 20 to 74, with an acceleration in the 60s and 70s. Significant changes in gene expression were seen in 5,600 genes, with 2,100 epidermal genes identified that were associated with younger-appearing skin. Genes associated with younger-appearing skin that were increased in expression were frequently linked with protective factors such as DNA repair, response to oxidative stress, cell replication and protein metabolism. Study participants who were slow agers with younger-appearing skin had gene expression profiles similar to those in younger cohorts. There were also notable decreases in expression of genes related to mitochondrial structure and function associated with increasing age, affecting the mitochondrial membrane, matrix, lumen and ribosome. Genes including *CDH1* and *DSC3*, which both contribute to cell-cell junctions in the epidermis, and *LAMA5*, which aids in the basement membrane attachment of keratinocytes, were all significantly increased in younger-appearing skin.[35]

The role of extrinsic aging due to UV light and gene expression appear to be linked in many regards. This connection is shown in an increase of cyclin-dependent kinase inhibitor 2A gene (*CDKN2A*) expression in women who reported above average sun exposure over their lifetime compared with those who reported average or below average sun exposure. *CDKN2A* codes for p16INK4a are associated with an induction of cell senescence and decreased cell replication, both contributing factors in skin aging. *CDKN2A* expression levels were relatively unchanged in photoprotected areas, such as the buttocks, and were notably higher in sun-exposed areas. Sun exposure contributes to changes in the natural protective mechanisms of the cell and is not only evidenced by the differences between slow, average, and fast skin agers, but is also seen in the histologic

changes in dermal elastosis seen in sun-exposed skin samples compared with sun-protected samples.[35]

To further understand the pathways affected by chronologic aging versus photoaging, a comparison was done using transcriptomic data from sun-exposed and sun-protected skin in young and old individuals. The analysis revealed reduced expression of genes related to managing oxidative stress, lipid biosynthesis, and epidermal differentiation in both chronologic and photoaged skin. The main differences in gene expression between chronologic aging and photoaging were reduced interstitial collagen genes in the chronologic aging group and increased elastic tissue genes in the photoaging group.[36]

Additional studies investigating changes in gene expression in aging skin have identified additional players in the aging process. One such study examined genes associated with intrinsic skin youthfulness in women aged 18 to 89 years, with the intent of identifying protective gene pathways. Whole transcriptome sequencing of the skin was conducted and samples were arranged by clinical skin appearance and by chronologic age, creating a gene expression profile for skin youthfulness. The study identified several candidate genes associated with skin youthfulness.[37] Similar to other human aging studies unrelated to the skin, the most significant changes in gene expression patterns occurred around the age of 40.[38,39] The primary domains of gene expression changes were found in cell adhesion, immune response dysregulation, and extracellular structure organization. The gene *PHLDA1*, involved in the antiapoptotic effects of insulin-like growth factor-1, was notably lower in patients with skin youthfulness compared with the non–skin youthfulness group. When analyzing changes in gene sets, an immunologic gene set was the most significantly altered in patients with skin youthfulness, identifying the immune system as a potential contributor to youthful appearing skin.[37] Multiple gene expression changes that are associated with skin youthfulness and intrinsic and extrinsic skin aging have been identified, and they provide many targets for additional investigation and potential future treatments to slow the aging process.

MicroRNA

Although the role of microRNA (miRNA) in skin aging has not yet been extensively studied, miRNA may play a significant role in regulating the aging process in the epidermis and dermis. miRNAs are noncoding, single-strand RNAs that regulate posttranscriptional gene expression through the degradation or transcription inhibition of target messenger RNAs. Early mice studies have shown that decreased miRNA production may contribute to skin aging and cellular senescence.[40] To better understand the role of miRNA in chronologic epidermal aging, an extensive transcriptional analysis was performed to identify differentially expressed miRNAs in keratinocytes during the aging process.[41] Keratinocytes were harvested from skin biopsies from healthy individuals in three age groups, including infants aged 3 to 6 years (n = 4), young adults aged 20 to 40 years (n = 4), and older adults aged 60 to 71 years (n = 4). Numerous miRNAs with age-dependent expression were identified, including 60 miRNAs with greater than 1.5-fold change in expression among at least two of the three groups.[41]

Genome-wide expression analyses were compared among age groups to assess for differential miRNA expression and identified age-related induction of miR-30a-3p and miR-30a-5p. Further, multiple gene targets of miR-30a in keratinocytes were identified, including *AVEN*, *IDH1*, and *LOX*. These genes were repressed by miR-30a overexpression in aged keratinocytes. *AVEN* encodes a caspase inhibitor that contributes to antiapoptosis, *IDHI* encodes isocitrate dehydrogenase 1 that plays an antioxidative role, and *LOX* encodes lysyl oxidase, an enzyme that assists in connective tissue maturation. Therefore, decreased expression of these genes as a result of miR-30a–induced effects may partially explain changes associated with aging. The overexpression of miR-30a in the older population impinged upon normal keratinocyte function and caused impaired differentiation and increased apoptosis in the epidermis. Similar findings were observed in an *in vitro* model of a reconstructed epidermis, further suggesting that miR-30a overexpression is implicated in common changes seen in skin aging.[41]

While miR-30a seems to be heavily involved in skin aging, other miRNAs induced in aged keratinocytes have been observed, including miR-138, miR-181a, and miRNA-181b.[42] In a study evaluating 88 miRNAs involved in skin cell differentiation and development, increased miR-124 expression was found in senescent skin compared with youthful skin. This increase, however, was found to be induced only with UVB exposure and did not show a significant increase when photoprotected senescent skin was compared with similar youthful skin. This finding suggests that increased miR-124 levels are unlikely due to intrinsic aging.[43] Another study evaluating 25 upregulated and 15 downregulated miRNAs in the aging dermis, identified miR-34 and miR-29 as two families of miRNA upregulated in skin aging. One role of the mi-R34 family is interaction with the p16 pathway that may promote senescence in intrinsic aging. Further, the miR-29 family is involved in cell senescence and cell proliferation, and it may play a part in extracellular matrix remodeling.[44]

At this time, there are still limited numbers of studies that focus on the role of miRNA and affected gene targets in skin aging. As the gene expression changes seen in skin aging are better cataloged and understood, miRNA involvement will contribute crucial information in the underlying mechanisms of these changes and provide additional targets for potential treatments to slow or halt the skin aging processes.

Mitochondrial depletion

Mitochondrial DNA (mtDNA) depletion and dysfunction are associated with aging and aging-related diseases.[45–48] This has been shown in several organs and organ systems,

including the skin, in both animal models and in humans. In a recent study, researchers were able to deplete mice of mtDNA via a doxycycline-inducible dominant-negative mutation in *POLG1*. Administration of doxycycline and mtDNA depletion subsequently led to a decreased number and activity of oxidative phosphorylation complexes. Further, this mutation induced a clinical phenotype characterized by wrinkled, inflamed skin, and hair loss, suggesting that mtDNA depletion may promote skin aging.[49]

Using reverse transcriptase polymerase chain reaction, the authors demonstrated that the mutant mtDNA-depleted mice had increased expression of certain inflammatory genes and matrix metalloproteinases. These mice also had decreased expression of tissue inhibitor of metalloproteinase 1 (TIMP1). The balance of these enzymes is important in maintaining collagen, and dysregulation of these enzymes can lead to wrinkle development. Interestingly, when doxycycline was held, mtDNA was restored to normal levels and the wrinkles and hair loss findings were reversed.[49]

Other murine models have abnormalities in mtDNA that also cause skin inflammation. For example, mice with mutant K320 E-TWINKLE, a mitochondrial helicase, develop mtDNA depletions and deletions. These mice further demonstrate altered stoichiometry and impaired activity of respiratory chain complexes within the epidermis and on a gross level, resulting in severe skin inflammation. In contrast to the *POLG1* model, however, in this model the inflamed skin was more reminiscent of psoriasis. Unfortunately, the mice in this study quickly died, on average within 5 to 8 days after birth, likely caused by secondary to impaired mitochondrial function and hypoglycemia, which prohibited a long-term aging study. Nonetheless, this study shows an association between mtDNA deletions and skin inflammation.[50] Further, the authors note that inflammation is thought to contribute to propagation of aging, potentially also skin aging, via a process coined "inflammaging."[50,51]

One particularly vital component of the mitochondrial genome appears to include a region of mtDNA (4,977 base pairs long) that, once deleted, is referred to as the "common deletion."[47,52] The common deletion includes DNA coding for components of the respiratory chain, including complexes I, IV, and V, which, when deleted, lead to impaired mitochondrial function.[47] *In vitro* exposure of human fibroblasts to UVA radiation promotes generation of the common deletion. This correlates to impaired activity of mitochondria, including decreased oxygen consumption, impaired mitochondrial potential, and decreased adenosine triphosphate content. Subsequently, increased expression of matrix metalloproteinase 1 (MMP-1) occurred without any concurrent change in TIMP1. Creatine supplementation, interestingly, was protective against these effects of UV radiation.[53] MMP-1 and TIMP1 are enzymes involved in collagen synthesis and degradation, and they provide a possible link among UV radiation, mtDNA depletion, collagen degradation, and the development of wrinkles and photoaging.[52,53]

In that study,[53] however, it was unclear whether increased expression of MMP-1 was a consequence of mtDNA depletion or UV radiation. To elucidate the root cause of increased MMP-1 expression, one group controlled for UV radiation by inducing mtDNA depletion in fibroblasts by exposure to ethidium bromide. Again, mtDNA depletion was associated with impaired mitochondrial function and increased expression of MMP-1. Concurrently, altered expression of other genes involved in the synthesis of fundamental dermal network proteins was observed. The authors proposed that mtDNA depletion and subsequent impaired mitochondrial function, a "defective powerhouse," causes oxidative stress modulating gene expression and lead to physiologic changes that are responsible for aging.[52]

Findings suggesting a role for the common deletion in skin aging have also been executed in human studies. *In vivo*, the common deletion is more common with age and, in one study, was not observed in the skin from participants under the age of 60. Importantly, while more common in the elderly, the common deletion is not always present in older individuals. Of study participants older than 70 years, approximately 40% did not have the common deletion present in their skin. The incidence of the common deletion was also more common in sun-exposed skin.[47]

These findings were replicated in another study that demonstrated that the concentration of the common deletion increased in neck skin samples with increasing age. The authors further showed that sun-exposed skin has a higher concentration of the common deletion compared with photoprotected skin. German women had a higher concentration of the common deletion in neck skin compared with Japanese women, although that finding was not statistically significant. Because Western cultures, such as the Germans, value tanned skin in contrast with Japanese culture, which places esthetic value on photoprotected skin, the authors proposed that sun exposure may be associated with the common deletion. Interestingly, the common deletion concentration correlated with phenotypic characteristics associated with aging in Japanese women, in whom a positive correlation was seen between wrinkles and the common deletion. This association was not observed in German women, in whom higher common deletion concentrations were associated with fewer pigmented lesions.[48]

Future studies

Recent research has identified multiple changes occurring at varying levels of genetic organization, from SNPs to variable gene expression. These efforts have provided novel potential therapeutic targets to abate skin aging and promote skin youthfulness. An important avenue of future research should include evaluating skin aging across different demographic groups, ethnicities, and skin tones; these efforts are paramount as the literature has focused on restricted

populations, especially in GWAS analyses.[21] Further research on subjects of different backgrounds will solidify our understanding of the genetic underpinnings of skin aging.

Future comprehensive analyses knitting together the many changes observed across these studies will help identify the most important mechanisms in skin aging and highlight the most critical protective genetic signatures. As current research demonstrate that slow agers have gene expression profiles similar to persons in younger cohorts, future research may use and target these biologic processes in efforts to mitigate skin aging.

Ongoing research on the intrinsic causes of skin aging will help harness these findings into new techniques to slow the skin aging process and maintain youthful-appearing skin. Despite notable overlap between intrinsic and extrinsic causes of skin aging, isolating gene expression changes unique to each will provide insight on the key pathways in skin youthfulness. Efforts to evade extrinsic factors that contribute to skin aging, such as sun and UV damage, include physical and chemical barrier sunscreens, protective clothing, and sun avoidance. Sun protection will likely remain the single most important factor in reducing overall skin aging, but additional intrinsic protective factors may supplement the effectiveness of sunscreens and reduce the harmful effects of the sun's rays. Additionally, once slow and accelerated skin agers are identified, evaluation of skin cancer rates among populations will help identify whether overlapping protective factors between youthful skin and lower risk of skin cancers exist.

Conclusions

Recent studies investigating the genetic mechanisms that underlie dermal aging have clearly made strides in the scientific pursuit toward maintaining youthful skin over time. Further research is warranted to uncover which genetic mechanisms have the strongest impact on skin youthfulness and which are potential targets for therapeutic intervention. Future exploration undoubtedly has exciting potential to enhance our understanding and ability to treat aging skin.

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