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Research Article

Epigenetic Regulation of Extracellular Matrix Remodeling in Skin Aging: Mechanisms and Interactions

Jiguang Yang, Yusong Shi and Xiaoqing Yan

Department of Medicine, Jinan Dermatosis Prevention and Control Hospital, Jinan, China

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Corresponding Author:
Yusong Shi
Medicine, Jinan Dermatosis Prevention and Control Hospital, China
Email: jiaqiyan1@outlook.com

Abstract: Skin aging results from complex interactions between genetic factors, environmental stressors, and epigenetic modifications that regulate extracellular matrix (ECM) remodeling. Accumulation of senescent cells impairs tissue regeneration through mechanisms including telomere shortening, reactive oxygen species accumulation, and ultraviolet (UV) radiation exposure. While epigenetic pathways regulate skin homeostasis, regeneration, and senescence, the specific epigenetic changes occurring during UV exposure, chronological aging, and neonatal development remain incompletely characterized. This study examined transcriptomic profiles of human skin tissues across developmental stages (neonatal to adult), chronological aging, and various UV exposure conditions using bioinformatic analysis in R (version 4.0.3). Significant epigenetic landscape alterations were identified during skin development, including changes in histone modifications, genomic imprinting, and N6-methyladenosine (m6A) RNA modification. These epigenetic changes primarily affected collagen synthesis, ECM organization, immune function, and keratinization pathways. Key epigenetic effectors regulating ECM architecture included IGF2BP2, GATA2, GATA3, CPA4, and CDK1, while immune function correlated with VEGFA, CDK1, and PRKCB expression. The m6A reader proteins (IGF2BP2, IGF2BP3, HNRNPA2B1, EIF3G) showed strong associations with antigen processing and presentation pathways. UV exposure, even at minimal erythema-inducing doses, altered expression of epigenetic effectors controlling ECM architecture, cell-matrix adhesion, innate immunity, mitochondrial function, and mRNA processing. Notably, UV-induced epigenetic alterations were more pronounced in aged versus young skin. Analysis of progeroid syndrome patient skin revealed molecular signatures resembling naturally aged skin, validating these models for aging research. These findings demonstrate that histone modifications, genomic imprinting, and m6A modifications play essential roles in skin development and aging, with UV exposure accelerating age-related epigenetic changes. This study provides a framework for understanding epigenetic mechanisms underlying skin aging and potential therapeutic targets.

Keywords: Skin Aging, Epigenetic Regulation, Extracellular Matrix Remodeling, Histone Modifications, N6-Methyladenosine, UV Radiation, Transcriptomics, Cellular Senescence

Introduction

The buildup of aged fibroblasts in the dermis is the primary cause of the age-related decline in skin texture and appearance. By way of an inflammatory histolytic senescence-associated secreted phenotype, senescent cells engage in aberrant remodeling of collagen and the extracellular matrix (Tsitsipatis, Gorospe, and Herman, 2022). The creation of potent skin anti-aging medicines relies on suppressing SASP in senescent cells. The function of the extracellular signaling molecule ectonucleotide pyrophosphatase phosphodiesterase

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member 5 in SASP is unknown; however, it has been linked to vascular aging and apoptosis [2] (He et al., 2020).

The ECM is a crucial part of tissues because it serves as a framework for the tissue and as a substrate for many metabolic activities. Its make-up is highly controlled, and any deviations from the norm may lead to the experiencing a progressive rise in skin illnesses associated with including cancer.papillomavirus, experiencing a progressive rise in skin illnesses associated with genetic material, is a necessary overall aging processpapillomavirus, experiencing a progressive rise in skin illnesses associated with genetic material, is a necessary overall aging process Horses are moexperiencing a progressive rise in skin illnesses associated with genetic mateoverall aging processy condition for related to aging because cutaneous homeostasis is becoming increasingly imbalanced. Inflammation caused by aging skin may spread to other parts of the body and has the potential to accelerate the aging process overall. Thregulation. They play a vital role in maintaining homeostasis and regulating fluid balance. Lymphatic endothelial cells, particularly VE-cadherin, have fewer adhesion connections, resulting in a decrease in the total number of lymphatic vessels and their activities in intrinsically aged skin (Liu et al., 2024). To remodel tissues throughout development, homeostasis, aprimary structural tasks—play critical roles. The structural function of several extracellular matrix proteins, such as collagens, is supported by matricellular proteins found within skin compartments, even if their expression is minimal after birth [5] (MacPherson et al., 2024). The aging process impacts almost factors. The dermal fibroblast population provides the basis for the basic molecular pathways that underlie the skin's aging processes. Both the quantity and functional activity of fibroblasts decline significantly with age, as has been shown (Tekkela et al, 2023).extension, skin aging. Skin changes with age are caused by epigenetic modifications that influence gene expression, which in turn alter the structure, function, and content of the extracellular matrix (ECM).

Epigenetic Mechanisms in Skin Aging

- **Histone Modifications:** Chromosome shape and gene accessibility are affected by histone acetylation and methylation, which in turn affect the expression of genes that are involved in the manufacturing, degradation, as well as cell signaling pathways of extracellular matrix (ECM) components.
- **DNA Methylation:** Regeneration, ECM remodeling, and skin cell senescence-related gene expression may be influenced by changes in patterns of DNA methylation, especially at telomeres.
- **Non-coding RNAs (ncRNAs):** Alterations in collagen, elastin, and hyaluronan that accompany aging may be facilitated by microRNAs and long non-coding RNAs that control the production of ECM proteins.
- **Impact on ECM Remodeling:**
- **Hyaluronan:** Hyaluronan production and breakdown may be influenced by epigenetic control, which in turn affects skin hydration as well as the structure and function of the ECM as a whole.
- **Collagen and Elastin:** diminished collagen density and greater elastin breakdown may cause wrinkles andreduced skin elasticity due to epigenetic alterations that change the balance of collagen production and degradation.
- **Other ECM Components:** In addition to affecting the structure and elasticity of the skin, epigenetic alterations may affect modifications to the expression of matrix proteins like fibronectin.

Consequences of Altered ECM

- **Increased Vulnerability to Environmental Stress:** Skin becomes more vulchangesal aggressors such as pollution and ultraviolet light as the ECM undergoes changes.
- **Skin Wrinkles and Sagging:** Wrinkles, as well as sagging skin, are brought about by a reduction of collagen and elastin, as well as changes in skin moisture.
- **Impaired Wound Healing:** Impaired skin healing efficiency may be caused by changes in the content and structure of the ECM.
- **Epigenetic Regulation and Skin Senescence:** Senescent cells may accumulate in the skin due to epigenetic alterations, which further disturb ECM homeostasis and worsen age-related changes.
- **Therapeutic Implications:** By influencing the composition and function of the extracellular matrix, epigenetic processes may provide therapeutic opportunities for reversing or reducing the aging process of the skin.

The majority of people get chemotherapy-induced peripheral neuropathy when they take chemotherapy medicines such as paclitaxel (Taxol). Chemotherapy

may not alleviate the numbness, tingling, pain, and temperature sensitivity associated with this nerve degeneration disorder, which manifests in the extremities. Severe CIPN symptoms might necessitate stopping chemotherapy, which has a significant majortimpact on cancer patients' quality of life. Interactions between collagen fibers and other components of the extracellular matrix enable the skin to perform one of its most critical functions: mechanical protection. The production of collagen fisteps, involving a complex and multi-step procemay be compromised due to disruptions that can occur at any time, r, and ages more quickly, when abnormalities in collagen production are present in the clinic (Phillips, Stamatovic, Keep, and Andjelkovic, 2023). According to current knowledge of skin aging, a senescence-associated secretory phenotype is triggered when senescent fibroblasts aggregate in the dermis and subcutaneous fat, leading to aberrant tissue remodeling and extracellular matrix dysfunction [9] (Dees et al., 2020). Our outermost defense mechanism and biggest organ is the skin. Both internal and external factors, caused by the continual stress it experiences, contribute to its aging. Specific epigenetic alterations, senescent cell buildup, decreased cell proliferation/tissue renewal, a changed extracellular matrix, as well as a proinflammatory milieu that promotes unfavorable conditions, including the onset of disease, are all hallmarks of skin aging [10] (Turner et al., 2021).

Collagen fibers, through their interactions with other components of the extracellular matrix, provide one of the skinessential crucial tasks: protection from mechanical harm. The process of collagen fiber turnover is a multi-staged and intricate process. The connective tissue's mechanical characteristics could degrade due to potential disruptions at each step. Increased skin flabbiness and looseness, as well as early signs of facial aging, are clinical manifestations of illnesses that affect collagen production (Urciuolo, Passariello, Imparato, Casale, and Netti, 2022). Among the significant dangers to human health, inflammatory disorders have grown in recent decades due to factors such as rapid urbanization, age, and lifestyle changes. Metabolic processes involving extracellular matrix factors include matrix metalloproteinases with tissue inhibitors of metalloproteinases. Diseases associated with inflammation rely on them. Inflammation, oxidative stress, and growth hormones are among the variables that enhance MMP synthesis, which in turn leads to ECM remodeling (Kim et al, 2022).

The risk of developing multiple chronic diseases, including diabetes, heart disease, stroke, cancer, and cellular malfunction, increases with age due to a gradual but steady decline in cellular and, ultimately, organismal function (Khokhlenkova et al., 2024). The skin is the body's biggest organ and the first place that shows the effects of time. Some of these symptoms include abnormal pigmentation, sagging skin, dryness, lack of elasticity, wrinkles, and thin skin. Radiation from the sun or pollution are examples of extrinsic variables that hasten the onset of these characteristics, whereas time, heredity, and hormone shifts are examples of internal variables (Thrane et al, 2021).

Consideration of Environmental Factors in Skin Aging

Intrinsic genetic and epigenetic factors, together with extrinsic environmental stressors such as pollution, sun exposure, and oxidative stress, all play a role in the complex process of skin aging. Aging cells build up and release cytokines as well as matrix metalloproteinases that speed up the breakdown of collagen and elastin; this is a characteristic feature of the process. Lesions, wrinkles, and a diminished ability for the skin to regenerate are all outcomes of these alterations (Takaya and Kishi, 2024). One possible way to slow down the aging process and keep things in balance is to target these processes via antioxidant methods, epigenetic regulation, or senolytic treatments. The role of extrinsic aging, primarily caused by environmental factors, in skin aging is being increasingly acknowledged. The production of reactivactivates pathways that degrade tissues. Particulate particles and other pollutants can penetrate the epidermis, causing oxidative stress and inflammatory responses that accelerate the aging processto the publication of the first experimental data documenting modifications to DNA methylation upon aging, the idea that environmental and lifestyle variables can shape the organismal phenotype by creating epigenetic alterations had been circulating in the scientific community for some time (Podstawski et al., 2022). Because skin is constantly coming into contact with the outside world, it is vulnerable to a wide range of environmental dangers that may inflict mechanical, thermal, chemical, and other kinds of trauma that can disrupt epidermal differentiation. Furthermore, the skin undergoes normal life processes, including aging, since it is an inherent component of the body. The skin and epidermis trigger systems that help the body fight against or adapt to harmful environmental influences, and epigenetic factors are now known to play a role in these processes.

Epigenetic Regulation of Extracellular Matrix (ECM)

Important in development and cellular differentiation, epigenetic factors control transcriptional and post-transcriptional aspects of gene expression. Changes in DNA methylation and demethylation, as well as alterations to histones (such as methylation, acetylation, and phosphorylation), either enable or hinder the binding of complexes that remodel chromatin, thereby changing its shape and availability to the transcriptional machinery. Conversely, miRNAs either prevent mRNA translation or cause its cleavage. Extensive research is being conducted to determine the role of epigenetic processes in controlling epidermal differentiation. This review article sheds light on the role of epigenetic variables in keratinocyte development and their control of this process. Alterations that control stem cells are part of the broader field of epigenetics, which studies cellular and molecular changes linked to many branches of science. This research addresses heritable alterations in gene expression that do not alter the DNA sequence.

Related Work

The purpose of the research was to utilize molecular tools to investigate the role of the researchers examined the effects of SASP and aging on human skin fibroblasts following various treatments, including lentiviral overexpression of ENPP5, human recombinant ENPP5 (rENPP5), and siRNA-mediated ENPP5 knockdown. Furthermore, they studied the dermis of C57BL/6 mice to see what happened when ENPP5 was knocked down using siRNA. Human skin cells that had undergone replication-aging or other forms of DNA damage showed dramatically increased production of ENPP5 and SASP, and senescence was accelerated by treatment with human rENPP5 or lentiviral overexpression of ENPP5. When ENPP5 was knocked down using siRNA, SASP and other variables associated with skin aging were inhibited. Loss of ENPP5 in mouse skin also improved the age-related decline in subcutaneous fat tissue, as well as the panniculus carnosus muscle layer, along with collagen fiber thinning. Ultimately, their results suggest the possibility of developing anti-aging skin therapies by regulating ENPP5 expression to inhibit SASP in aging cells, thereby preventing age-related alterations.

Gene constructs producing the BPV1-E1~E4 protein were used to neoplastically convert adult cutaneous fibroblast cell lines and horse sarcoid tissue bioptates, demonstrating the unregulated expression of certain genes. Using the existing literature data, they were able to determine that the identified genes (CD99, ITGB1, JAM3, and CADM1) were either upregulated or downregulated, indicating phenotypic modifications compared to the backgrounds shown for appropriate expression patterns in other tumor types, both malignant and noncancerous. Their goal in conducting that work was to determine how disruptions to the ECM impact the sarcoid formation method by comparing the expression patterns of genes involved in ECM remodeling and the cell adhesion pathway . In addition, they compared dermal fibroblast cell lines that had been transfected or not via a construct encoding the E4 proteins of the BP virus, as well as with healthy skin-derived explants and equine sarcoid tissue bioptates, to find out how that construct affected ECM disorders. The data that were obtained provide significant evidence that genes linked to ECM are associated with the development of sarcoid (Raja, Clarin, & Yanagisawa, 2023).

Zorina, Zorin, Kudlay and Kopnin, (2022) also suggested further processes. Dysfunction of lymphatic arteries as a pumping mechanism may be associated with aging-related alterations in the extracellular matrix, an increase in reactive oxygen species, and disruptions in the eNOS/iNOS dynamic. The hyperpermeability of lymphatic arteries in skin that has been exposed to environmental aging is caused by a decline in endothelial-specific tight-junction molecules, an increase in VEGF-A, and a drop in the VEGFC/VEGFR-3 signaling pathway. Phytotherapeutics may also slow skin aging by influencing lymphatic vessel function. Lymphatic vessel dysfunction and its role in skin aging were reviewed in that study, along with anti-aging methods that target lymphatic vascular modulation.

The role of matricellular molecules in skin stem cell niches, which affect the destiny and self-renewal capacity of st. At the same time, TGFBI, which stands for transforming growth factor-βinduced protein ig-h3, boostspromotes the heterogeneity and fitness of epidermal stem cells even as they age. In contrast, TGFBI, which stands for transforming growth factor-β-induced protein ig-h3, enhances the proliferation of epidermal stem cells and their ability to repair wounds. Periostin, SPARC, fibulin 1, CCN2, as well as R-Spondin 2 and 3 are matricellular proteins found in the hair follicle stem cell niche.

The mechanisms behind these processe with a focus on the alterations that occur in the dermal stem/progenitor cells as they get older (Staff, Hrstka, Dasari, Capobianco, and Rieger, 2023). These cells comprise dermal fibroblastic differentiation and are responsible for forming the microenvironment, or

niches. The number of dermal fibroblasts, which are responsible for producing and modifying the dermal extracellular matrix, decreases as a result of these alterations because stem cell numbers drop. Molecular pathways of DNA damage response, cellular and systemic effects of DNA damages, and the part played by fibroblast senescence in skin aging are all well described.

The research aimed to develop a new skin-filling product. A novel skin-filling product derived from adipose tissue was created. They produced adipose collagen fragment by pulverizing, filtering, and centrifuging the tissue. Cell viability, structure, and macrography of ACF were assessed using immunostaining, Western blot, and cell culture tests (Potekaev et al, 2022). To study the skin filling capacity and collagen remodeling process, 36 female BALB/c nude mice were intradermally injected with ACF, nanofat, and phosphate-buffered saline (9 spots/side, 0.01 ml/spot). Twenty-one female patients were included in the clinical trials that used ACF to treat fine rhytides in the infraorbital regions. Assessments of therapeutic outcomes and patients' levels of satisfaction were documented.

The fundamental etiology of CIPN is a skin-specific degradation of the extracellular matrix, as previously shown in zebrafish and rat models of paclitaxel-induced peripheral neuropathy (Potekav et al, 2022). The purpose of that research was to examine the skin reactions of paclitaxel-treated breast cancer recipients with CIPN after the drug had been administered. On the distal leg of both healthy controls and CIPN patients ranging in age from 60 to 70 years, they conducted a skin punch biopsy. Skin samples from CIPN patients and controls showed comparable nerve fiber densities; however, RNA sequencing revealed substantial alterations in gene expression related to the cellular matrix, cytoskeleton, cell cycle regulation, and genes implicated in nervous system function. Immunostaining revealed collagen degradation and the basement membrane thinning at the ultrastructure, while MMP-13, an enzyme that breaks down extracellular matrix, was found to be expressed at an enhanced level in the skin of CIPN patients. Results like these suggest that CIPN after paclitaxel treatment could be due in part to extracellular matrix remodeling. One dose-limiting adverse effect of the chemotherapy drug paclitaxel is peripheral neuropathy, which affects as many as 68% of cancer patients. The current review compiles and organizes the existing literature on the topic of genetic, along with epigenetic variables, as they pertain to the skin's collagen fiber production (Takaya, Asou and Kishi, 2022). By delving into the causes of diseases related to collagen production, medical professionals may offer treatments that are based on pathogens, ensuring maximum effectiveness while minimizing side effects.

Finding particular protein indicators for senescent cells is necessary for a unique therapeutic method to prevent skin aging, which is to eradicate senescent dermal fibroblasts (Potekaev et al, 2021. Apolipoprotein D (ApoD) is highly expressed in tissues impacted by age-related disorders including atherosclerosis and Alzheimer's disease, and it plays a role in lipid metabolism as well as antioxidant responses. However, how it acts and its role in skin aging remain unknown. Using aging models in human dermal fibroblasts, they tested the hypothesis that ApoD serves as an indicator of age. The expression oandD was increased at both the created through replicative aging and exposure to ionizing radiationgh replicative aging while ionizing radiation exposure. That upregulincreased uptake of the proliferation marker BrdU, as well asgalactosidase activity, reduced ptake of the proliferation marksuggest that ApoD may serve as a potential clinical indicator for identifying cutaneous fibroblasts that are undergoing suggest that ApoD may serve as a potential clinical indicator for identifying cutaneous fibroblasts that are undergoing clinical indicator for detecting cutaneous fibroblasts that are aging.

Scientists compiled and organized all the data on the impact of epigenetic and genetic variables on the turnover of collagen fibers in the skin (Dermitzakis et al, 2025). Additionally, they zeroed in on the several collagen types found in skin and the roles they play. Doctors can administer pathogenetically based therapies, get the best outcomes, and limit side effects if they understand the cause of decreased collagen production. The active substances and methods of action of botanicals are not as well understood, despite their long history of usage in diverse cultures for the treatment of inflammatory disorders, wound healing, and skin beauty preservation (Szabó et al, 2025). It is well established that environmental factors and dietary components influence gene expression at various stages of life. The fact that our "epigenome" records our exposure to certain phytochemicals and how they impact gene expression through reversible epigenetic pathways is a relatively new finding. Changes in DNA methylation, chromatin structure, or microRNA profiles

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are the basis of heritable phenotypic variances or changes in gene expression that are referred to as epigenetics. Dietary epigenetic imprints on genomes may modify host immune system gene expression protection against inflammatory diseases, cancer, and aging. The search for potential nutraceuticals or cosmeceuticals that can aid wound healing, skin regeneration, tissue homeostasis, (re)program stem cell differentiation, or "correct" epigenetic marks that cause inflammatory skin disorders and ageing has recently begun, thanks to this renewed interest in the epigenetic effects of nutritional, botanical, or phytopharmaceutical substances.

For the purpose of establishing and maintaining normal skin functioning, the authors of the publication summarize what is currently known about various epigenetic changes and their roles (Orioli and Dellambra, 2018). These systems enable the tight regulation of gene expression in normal skin, which in turn allows for a dynamic equilibrium between cell differentiation and proliferaton, as required for efficient barrier function. Epigenetic mark changes can contribute to a decrease in skin regeneration ability and an increase in sensitivity to environmental stresses with aging. To further illustrate how microbial communities impact skin health by regulating host gene expression, we will also investigate the relationship between epigenetic regulation and the skin microbiome. Longevity, resilience, and healthy skin development in the face of environmental change should be the goals of future studies. Because of this, investigating these intricate regulatory networks requires the use of integrative methods.

According to Lesniak (2024), as we age, our skin's ability to regenerate naturally decreases. Aged skin is likely a result of impaired tissue regeneration caused by the gradual buildup of senescent cells. Several internal and external factors, including as telomere shortening, an excess of reactive oxygen species, food, and sun exposure, cause keratinocytes & dermal fibroblasts to age. In addition to regulating homeostasis and regeneration in the skin, epigenetic pathways also indicate cell senescence and both normal and abnormal aging. Skin and other organs age more quickly in a set of clinically and genetically diverse diseases known as progeroid syndromes. The molecular characteristics of skin cells from progeroid individuals resemble those of naturally aged skin. Researchers have made significant strides in understanding the underlying causes of aging via their work on progeroid disorders (Zhang et al, 2article. This article explores the role of epigenetic systems in regulating skin cell function during both normal and accelerated aging.

Epidermal differentiation is an essential process for the upkeep of the epidermis in both normal and abnormal skin states, as well as in response to stress and other skin diseases. Gene expression is tightly regulated during epidermal differentiation. Epigenetic processes, such as covalent histone modifications, DNA methylation, as well as miRNA activity, modify chromatin accessibility and mRNA stability, and hence regulate different steps of gene expression. There has been a lot of research into their role in epidermal differentiation, and what we know so far points to a web of epigenetic factors and transcriptional regulators that works to keep the epidermis in a stable state and protect it from harmful environmental stresses.

Methods and Materials

We searched the GEO public databases for transcriptome information relating to human skin samples irradiated with various kinds and dosages of UV radiation, or from different ages. Five high-quality array datasets (GSE181022, GSE18876, GSE56754, GSE52980, and GSE22083) were obtained. Data on exposed skin from various age groups may be found in GSE181022 and GSE18876. Data on younger people's skin that has been exposed to various forms of ultraviolet radiation (UVB, UVA+UVB, UVA, sub-minimal erythema dosage) can be found in the GSE56754 dataset, while data on older and younger people's skin that has been subjected to or not exposed to sunlight can be found in GSE52990. Furthermore, GSE22083 was also included, which contains information on skin that has been subjected to the MED dosage of solar-simulated radiation (SSR). For each dataset, Table S1 displayset,. Table 1 shows detailed information about the transcriptome results. Additional resources, such as primer sequences for quantitative polymerase chain reaction are given in Table 2. The manner in which the levels of gene expression are distributed among the various GEO datasets. Boxplot and densityplot are the two types of plots which is given in Fig 1 (a) and Fig 1(b).

Table 1: Brief information of transcriptome data

GEO accession	Simple source	Source type	Simple sizes	# of genes included	Normalized Values	Platform	Group included	Treatment
GSE181022	Human skin	Array	70	19,912	15122	GPL13667	Infant (n=27, 30.7-89.1 week), young (n=25, 20-24 year), elderly (n=18, 60-64 year)	No
GSE18876	Human skin	Array	98	17,324	15236	GPL5175	Young (n=25, 19-39 year), middle-aged (n=29, 41-54 year), elderly (n=44, 55-86 year)	No
GSE56754	Human skin	Array	132	19,595	17485	GPL6480	Control_t14 (n=7), SSR_t14 (n=7), UVA_t14 (n=7), UVB_t14 (n=7) age 37.3 ± 15.7	Control: NO, SSR: irradiated with UVA+UVB radiation for 2 weeks, UVA: irradiated with UVA radiation for 2 weeks, UVB: irradiated with UVB radiation for 2 weeks
GSE52980	Human skin	Array	16	22,880	21556	GPL570	Sun-exposed elderly (n= 4, over 60 years old), sun-protected elderly (n= 5, over 60 years old) sun-exposed younger (n= 4, under 35 years old), sun-protected younger (n= 3, under 35 years old)	Sun-protected biopsy specimen from the upper inner arm, sun-exposed specimen from either the dorsal forearm or crow's feet (lateral epicanthus)
GSE22083	Human skin	Array	98	13,237	12425	GPL96	Control (n=14), 1 MED ssR (n=14), 19-36 years of age	Control: NO, 1 MED ssR: exposed 1 minimal erythema dose (MED) of solar-simulated radiation (ssR)

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Table 2: Supplementary material -qPCR primer sequences

Gene	Primer	Sequence
COL1A1	Forward primer (FP)	GTGAGAGAGGTCGCCCTGGA
	Reverse primer (RP)	CCCGGCAGCACCAGTAGC
IGF2BP2	Forward primer (FP)	CTACGCCTTCGTGGACTACC
	Reverse primer (RP)	TGTGTCTGTGTTGACTTGTTCC
GAPDH	Forward primer (FP)	CTCTGCTCCTCCTGTTCGAC
	Reverse primer (RP)	GCCCAATACGACCAAATCC

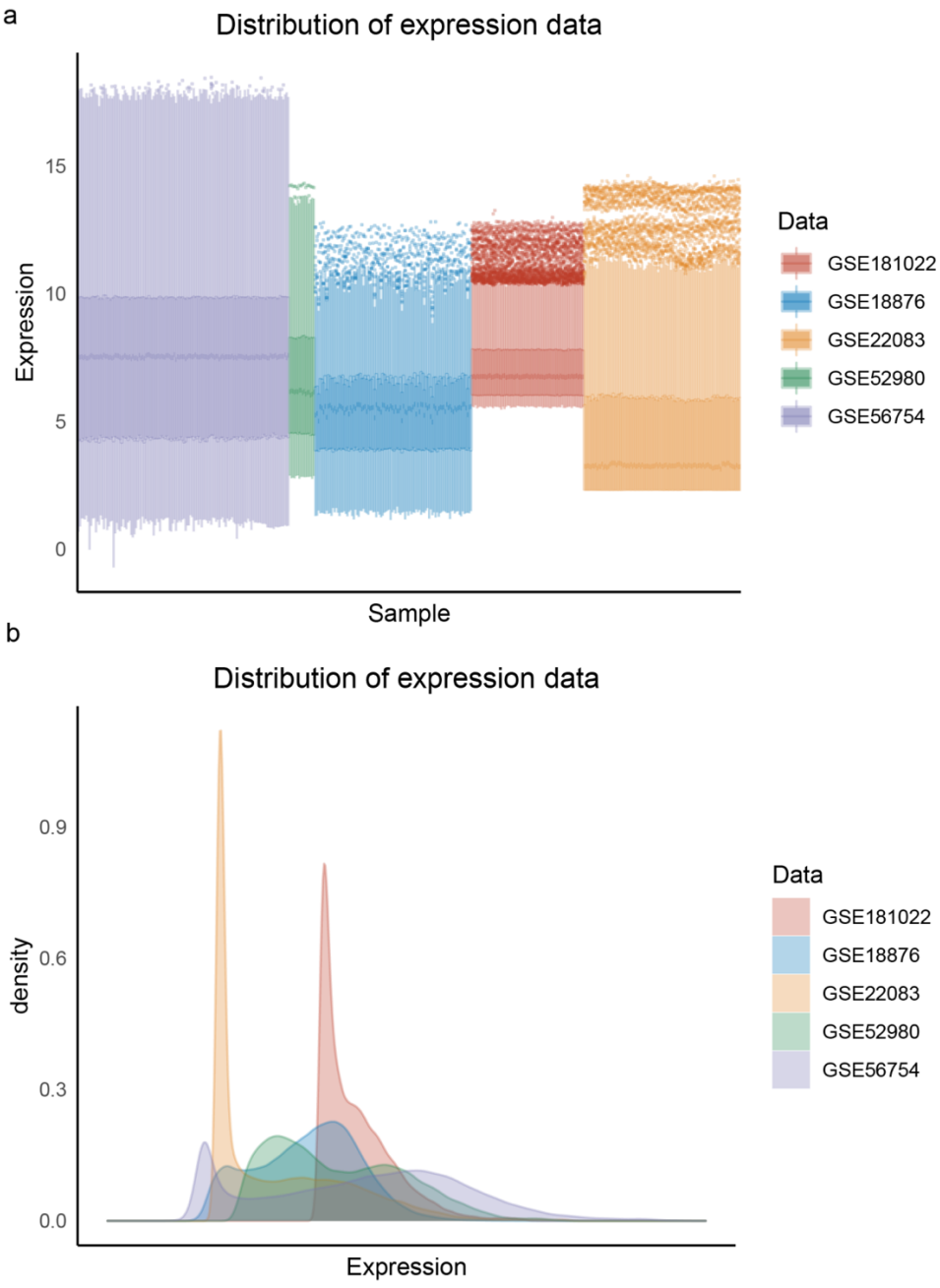

Fig. 1: The distribution of gene expression levels in different GEO datasets. a. Boxplot, b. Densityplot

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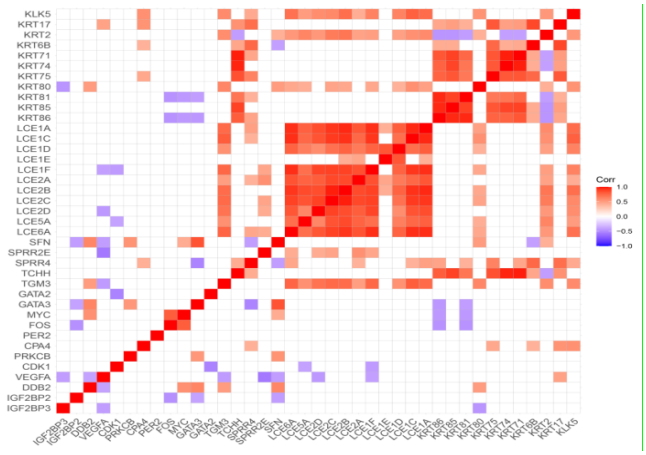

Fig. 2: Epigenetic effectors with Keratinization

Fig 2 shows the mechanism via which epigenetic effectors contribute to keratinization. Top epigenetic mechanisms and keratinization functional sets genes' correlation study. In order to analyze correlations, the "pearson" approach was used in which"corr" only means correlation**.**

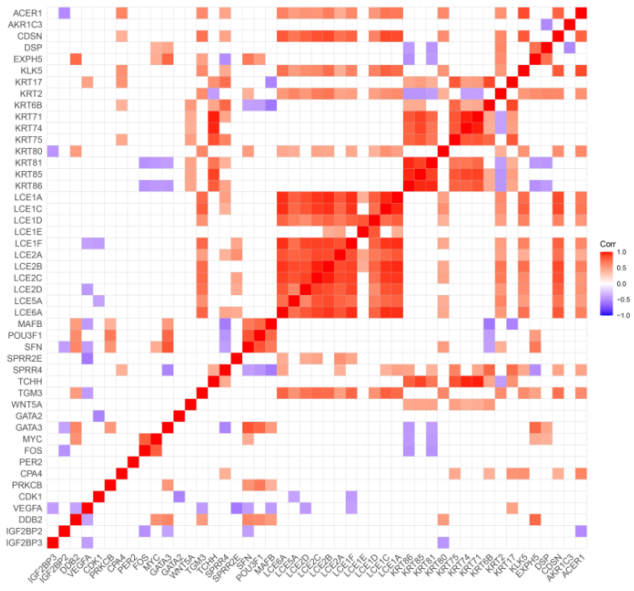

Fig. 3: Keratinocyte Differentiation with Epigenetic Effectors

As shown in Figure 3, keratinocyte differentiation is associated with epigenetic effectors. Correlation study of key epigenetic effectors with genes in the functional categories of keratinocyte differentiationto analyze correlations, the "pearson" approach was used. "corr" only means correlation.

The top GO findings of DEGs showed a strong correlation with APOBEC3C (Fig. 4). The DEGs and APOBEC3C correlation coefficient was denoted as Cor.

We may see the correlation coefficient as a gradient in color.

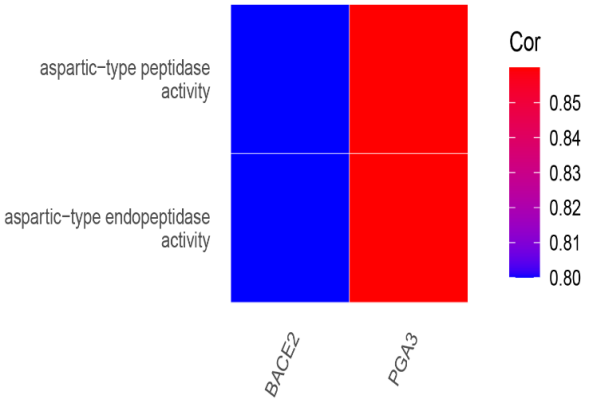

Fig. 4: Element APOBEC3C Correlation

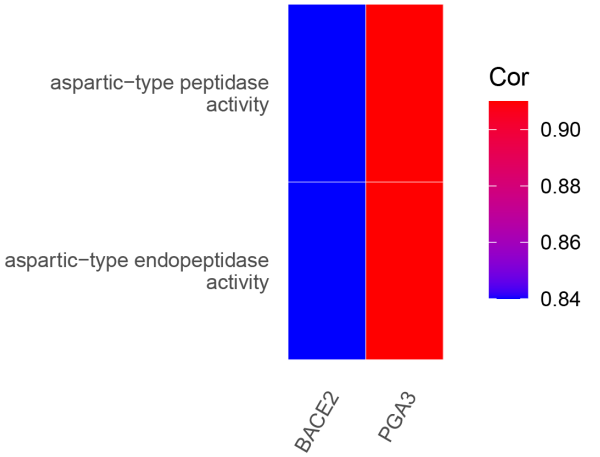

Fig. 5: Linked Top GO Findings for DEGs with APOBEC3F. The most significantly linked top GO findings for DEGs with APOBEC3F were highly positive. The correlation coefficient (Cor) between APOBEC3F and DEGs was displayed. We see the correlation coefficient as a gradient in color.

Methods

Machine learning algorithms have the ability to sift through extensive information pertaining to skin, such as imaging data, gene expression levels, and protein levels, in order to deduce and forecast how skin ages. Improved skin health and appearance can be achieved by targeting extracellular matrix (ECM) remodeling using this strategy. It can help discover particular peptides or chemicals that can do this. To find bioactive peptides (matrikines) containing medicinal potential, ML algorithms can foretell where common matrix proteins could be "cut" by skin enzymes. Machine learning (ML) can sift through mountains of skin sample

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proteins and genetic expression data in search of age- and disease-related patterns and biomarkers. With the use of ML, we can create models that can anticipate how a person's skin will age and how they would react to various treatments depending on their specific traits. Machine learninmultiple sources, thereby aiding in the development of tailored treatments. Machine learning (ML) has the potential to revolutionize the search for anti-aging medicines by rapidly sifting through mountains of data in search of critical molecular actors. Based on these findings, it appears that the immune microenvironment may undergo significant changes as a whole due to age-related physical alterations in the ECM, which can enhance tumor cell motility but may have the opposite effect on the motility of certain immune cells. More effective treatment options for elderly melanoma patients may emerge if our comprehension of the physical modifications in skin aging is advanced.

The quantile, along with summary functions, was used to verify the distribution and mean value of the expression data. We eliminated samples with poor quality or genes with extremely low expression (more than 2000 genes). Analysis was conducted as a follow-up to quality control, as shown in Fig. 6.

Machine Learning

For this purpose, we choose distinctive disease diagnostic indicators using random forest and Lasso logistic regression techniques. The "glmnet" package is used by the Lasso method. The decision trees are the basis of the ensemble learning method known as random forest. It takes several samples from the original set and utilizes them as a training set using the sampling plus replacement technique. A decision tree is constructed using the data set acquired via sampling. The sample set is divided according to the non-repeating properties that are randomly picked on each created node. Locate the most effective dividing characteristics and ascertain the outcome of the forecast. In this research, the random forest method is used to rank the features according to their relevance using %MSE. Then, the top fifteen features are chosen for further investigation.

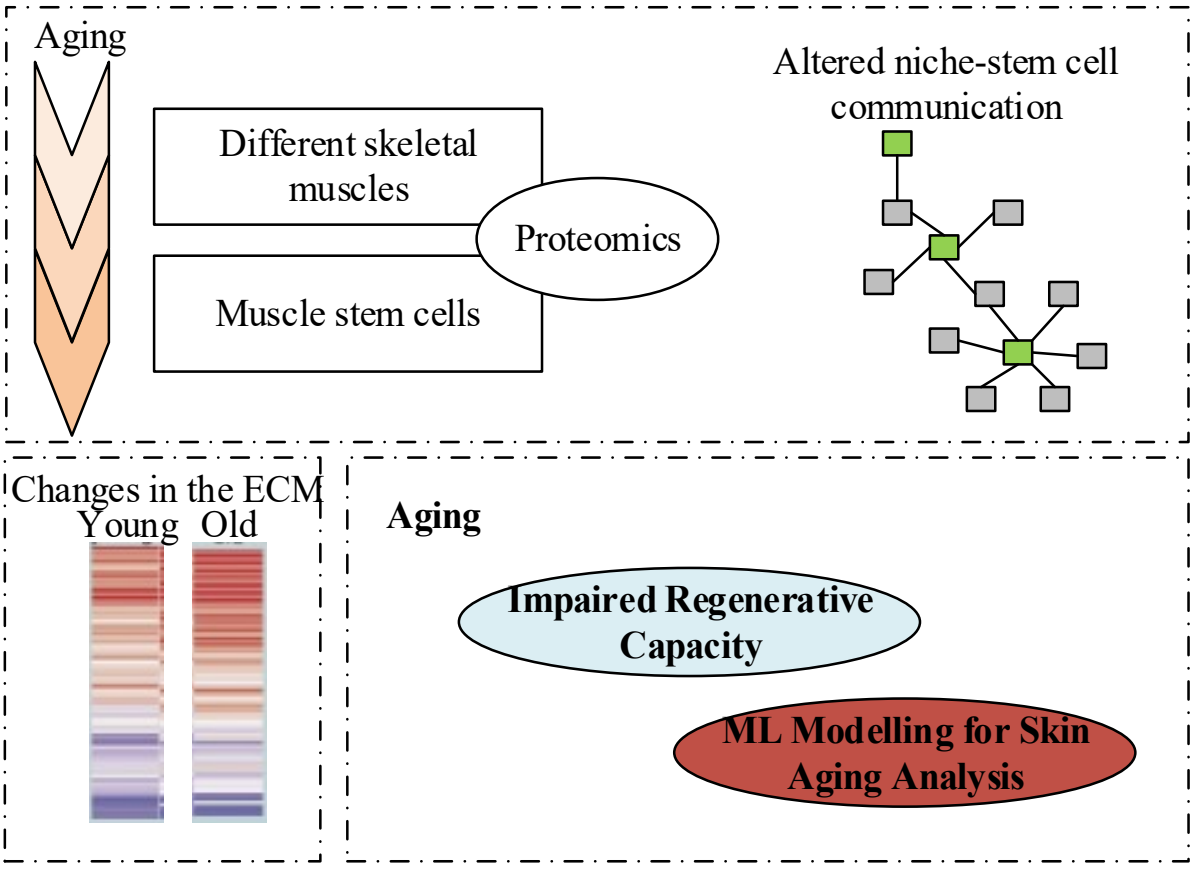

Fig. 6: Skin Aging Model

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Results and Discussion

We conducted the statistical analysis using R (version 4.0.3). Distribution box plots, correlations between samples, as well as t-SNE reduction were the primary metrics used to evaluate dataset quality. One method for exploring and visualizing high-dimensional data is t-SNE, which stands for t-distributed Stochastic Neighbor Embedding. It is an unsupervised non-linear dimensionality decrease approach. By using the technique for non-linear dimensionality reduction, we are able to partition data that would otherwise be inaccessible using a straight line. For the sake of subsequent analysis, expression levels were applied to both genes and samples; any NA (not available) data found in the expression matrix were manually replaced with 0.

Preprocessing, Data Normalization and Batch Correction

There are a lot of different approaches that try to enhance the data quality of DNA methylation microarray analysis, and it's not easy. Each of these steps—which may be roughly categorized as preprocessing, data normalization, or batch correction—might affect the final output. Image processing, methylation level calculations, quality control, and probe and chip filtering are all part of the initial phase, preprocessing. Normalization, the second stage, aims to eliminate technical variance within and across chips. Background correction, whichincludes dye bias correction, is frequently accomplished using the normal-exponential out-of-band (Noob) approach. Finally, there is the possibility of batch effects, which manifest as systematic differences between samples tested on various days, chip positions, or bisulphite conversion efficiencies.

Batch correction with ComBat is common practice. Warnings that using batch correction might disguise biological differences are common, however, as is the case with most batch correction procedures. To find any batch effects in the data we used, we used principal component analysis. Clustering of studies was seen in PCA, suggesting batch effects. Applying ComBat allowed us to circumvent these batch impacts. We started by including age as a protected variable and used the default strategy, which is the parametric version (i.e., each investigation becomes relative to each-other). Because of this, the independent test dataset and the training dataset were quite different (data not shown). Nevertheless, the two datasets were able to be compared after transitioning to "reference study mode" (modifying training and test data with the YFS study).

Evaluation of Prediction Performance

We built a R function to periodically execute elastic network cross validation so we could test out various processing pipelines: In this case, we utilized the cv.glmnet function from the GLMnet R-package (v4.1-3) with the minimal lambda value that was specified, the default loss measure, and alpha = 0.5. For the cross-validation process, we used a randomly selected training subset (representing since these data were not used in the cross-validation approach, we evaluated the constructed model's performance using the test dataset. As a result, the function had two sets of exam data. We applied the median absolute deviation metric, which represents the number of years between the projected and actual agewhich helps us evaluate our succassessess.valuate our success. A distribution of MAD scores was obtained by repeating the training and prediction processes 10 times. All samples were used as training data in the final model fitting, also known as the final predictor, except the independent twin test dataset, which is given Fig 7.

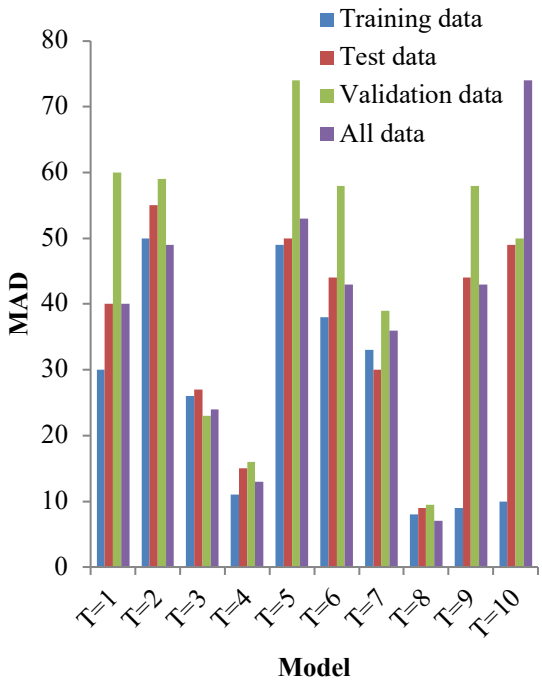

Fig. 7: MAD Analysis Model

Conclusion

The purpose of this research is to draw attention to the critical role that epigenetic changes play in the aging process and to investigate possible treatments based on

both Western medicine as well as Traditional Chinese Medicine. We illuminate new therapeutic avenues for controlling skin aging by collecting data on the medicines known to have epigenetic modulatory effects. There is significant therapeutic value in elucidating the role of epigenetic changes in skin aging, as this may pave the way for the development of novel treatment approaches that modulate epigenetic processes to halt or even reverse skin aging. Given that skin aging is a global concern, this work has significant implications for dermatology and aging research. It could lead to targeted interventions that modulate epigenetic processes to slow down skin aging and promote healthier skin overall. Additionally, this multidisciplinary study lays the groundwork for future research and clinical trials to confirm both the safety and effectiveness of such actions in treating skin deterioration caused by aging, by identifying possible therapeutic targets linked to epigenetic changes and by highlighting the efficacy of drugs that focus on the epigenetic modification level.

Ethics

The authors confirm that all the research meets ethical guidelines and adheres to the legal requirements of the study country.

Author Contribution

Jiguang Yang: Review & editing, Writing - original draft, Visualization, Data curation. **Yusong Shi**: Writing - review & editing, Writing - original draft, Methodology, Formal analysis, Data curation. **Xiaoqing Yan**: Writing - review & editing, Writing - original draft, Supervision.

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