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REVIEW

Epigenetic Clocks in Skin Aging: From Exposome Drivers to Biomarkers and Therapeutic Interventions

Alejandra DelaO-Escamilla[1], Samar Khalil[2], Hassan Galadari[3], Stefania Guida[4]

[1]Department of Dermatology, Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, Mexico; [2]Department of Dermatology, Skin and Scalpel Clinic, Beirut, Lebanon; [3]Department of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates; [4]School of Medicine, Vita-Salute San Raffaele University, Dermatology Clinic, IRCCS San Raffaele Hospital, Milan, Italy

Correspondence: Hassan Galadari, Department of Medicine and Health Sciences, United Arab Emirates University, Khalifa Bin Zayed Street, P.O. Box 15551, Tawam, Al Ain, United Arab Emirates, Tel +971-03-7137571, Email hgaladari@uaeu.ac.ae

Abstract: Skin aging is a multifactorial process driven by a combination of intrinsic genetic programming and extrinsic environmental exposures. Recent advances in epigenetics have illuminated how changes in DNA methylation, histone modifications, and non-coding RNAs regulate skin aging, with the epigenetic clock emerging as a powerful tool to quantify biological age. This review aims to synthesize current evidence on how environmental and lifestyle factors – particularly ultraviolet radiation, pollution, smoking, diet, and stress – accelerate skin aging through epigenetic mechanisms, while also evaluating the potential of skin-specific epigenetic clocks as biomarkers for early detection of premature aging and for guiding therapeutic interventions. We further discuss the expanding field of epigenetic-targeted therapies in dermatology, encompassing topical agents, energy-based devices, and systemic approaches that may reverse or delay visible signs of cutaneous aging. By integrating insights from molecular biology, environmental science, and clinical dermatology, this review positions skin aging not as an irreversible outcome but as a modifiable, biologically regulated process with promising avenues for personalized prevention and rejuvenation.

Keywords: epigenetic aging, skin rejuvenation, environmental exposome, DNA methylation, therapeutic interventions

Introduction

Skin ageing has shifted from a purely cosmetic preoccupation to a public health issue as life expectancy rises and more than two billion people are projected to be over 60 years old by 2050.[1] Clinically, visible changes such as wrinkles, pigment irregularities, or laxity erode quality of life.[2,3] Still, mechanistically, they reflect deeper molecular damage that accumulates daily with ultraviolet (UV) exposure, air pollution, diet, and lifestyle choices.[4,5] Over the past decade, epigenetic drift, which is the predictable, age-linked alterations in DNA methylation, histone marks, chromatin architecture, and non-coding RNAs,[6,7] has emerged as the crucial conduit through which those external insults are transduced into lasting changes in cutaneous gene expression.[8–10]

This epigenetic drift is quantifiable: pan-tissue and skin-specific "epigenetic clocks" translate thousands of methylations shifts into a biological-age read-out that correlates tightly with clinical photoaging scores and systemic morbidities.[11–13] Equally important, drift is no longer viewed as unidirectional; landmark work shows that transient expression of reprogramming factors, small-molecule inhibition of DNA and histone-modifying enzymes, and even clinical interventions such as fractional lasers can partially reset the cutaneous clock without erasing cell identity.[14–16] These findings recast skin ageing as a dynamic and potentially reversible epigenetic program rather than a fixed consequence of somatic mutation.

In recent years, skin epigenetics has advanced rapidly, illustrating how alterations in DNA methylation, histone modifications, and non-coding RNAs drive visible signs of aging. No longer viewed merely as passive markers of biological decline, these epigenetic changes are increasingly recognized as active contributors to age-related dysfunction

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in the skin. Therefore, a careful look at current evidence offers crucial insights into both the mechanistic basis of cutaneous aging and the therapeutic potential of targeted epigenetic interventions. Accordingly, this review synthesizes current knowledge on the epigenetic drivers of skin aging, emphasizing environmental factors and therapeutic strategies to clarify how targeted epigenetic interventions could transform future dermatologic care.

Material and Methods

This review was conducted through a comprehensive search of the PubMed database for English-language articles published between 2000 and 2025, using combinations of keywords such as *skin aging, epigenetic clock, DNA methylation, histone modification*, and *epigenetic therapy*. Additional relevant references were identified through manual screening of bibliographies from key publications. Studies were included if they examined molecular epigenetic mechanisms, environmental and lifestyle influences on cutaneous aging, or interventions with demonstrated epigenetic or rejuvenating effects in skin.

Results

Epigenetic Mechanisms in Skin Aging

Epigenetic changes drive skin aging by reprogramming gene activity without altering the DNA sequence. These modifications act as molecular switches, silencing regenerative pathways while activating inflammatory and senescent programs. Although DNA methylation is the best-studied layer, skin aging reflects an integrated network of DNA methylation, histone and chromatin remodeling, non-coding RNA regulation, and higher-order three-dimensional (3-D) genome architecture. Appreciating how these layers communicate is essential for designing interventions beyond single-target approaches (Figure 1).

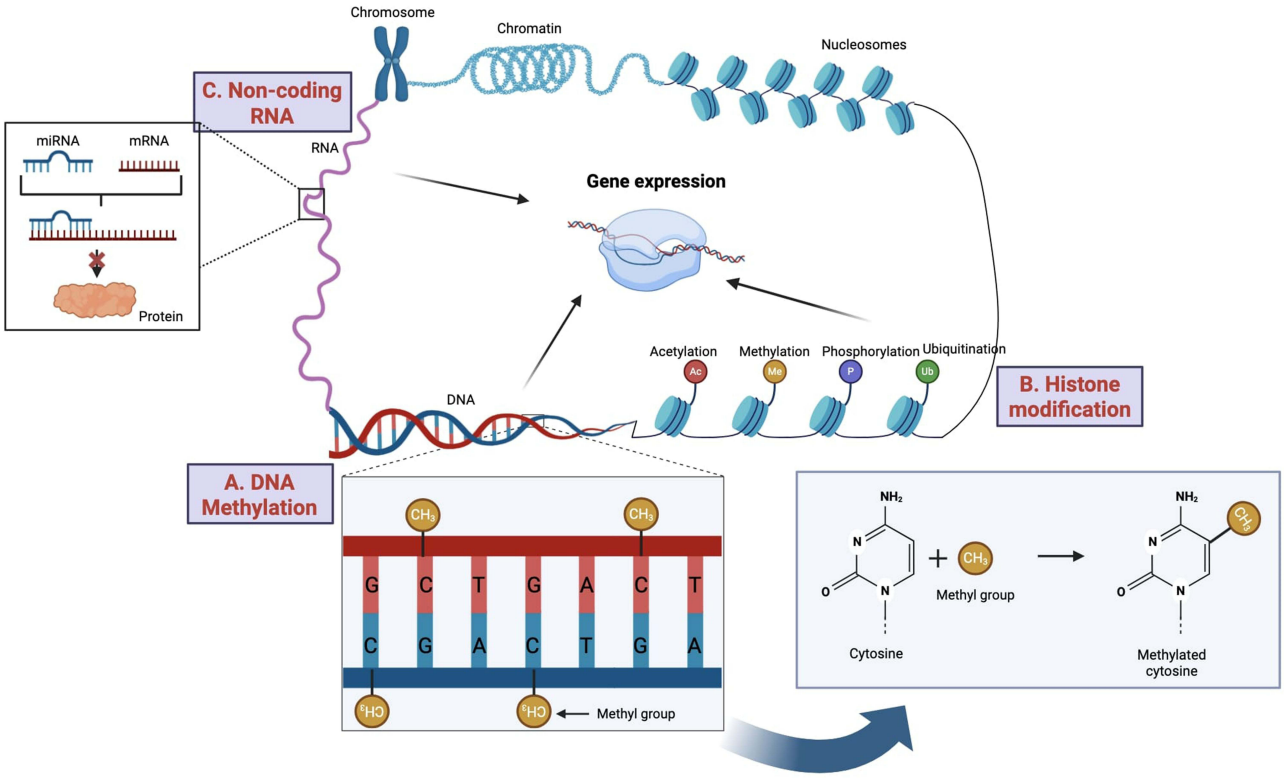

Figure 1 Epigenetic mechanisms underlying skin aging. Skin aging results from coordinated alterations in (**A**) DNA methylation, (**B**) histone modifications, and (**C**) non-coding RNA activity. These changes silence regenerative genes, activate inflammatory and senescence pathways, and reshape chromatin architecture, collectively driving the molecular and functional decline characteristic of aged skin.

DNA Methylation

Epigenetic changes significantly influence skin aging by altering gene expression without DNA sequence mutations. One primary process is DNA methylation, where chemical tags are added or removed at cytosine–phosphate–guanine (CpG) sites. Over time, the skin experiences a general loss of methylation across large genomic areas (global hypomethylation) and localized hypermethylation in specific regulatory regions.[9,17] During natural chronological aging, excessive methylation in CpG islands of genes tied to stem cell function and regeneration can silence these genes, reducing the skin's regenerative capacity.[8,9,18] Simultaneously, loss of methylation in other regions (eg, repetitive or heterochromatic DNA) can trigger genomic instability and unwanted gene activation. Enzymes such as DNA methyltransferase 1 (DNMT1) have been linked to age-related methylation changes,[19] including suppression aging-related loci like p16INK4a and upregulation of age-dependently silenced genes. However, DNMT1 levels naturally decline with age, thus potentially accelerating visible signs of aging.[20,21]

Equally relevant is the compensatory rise in ten-eleven translocation (TET) dioxygenase activity that converts 5-methylcytosine to 5-hmC;[22] photodamaged epidermis shows a paradoxical global drop in 5-hmC despite heightened local TET recruitment,[23] suggesting substrate depletion rather than enzymatic failure. These observations caution against blanket DNMT inhibition because widespread demethylation without synchronized 5-hmC maintenance can unmask transposable elements and destabilize the genome.[24] It remains controversial whether simply reversing focal hypermethylation is sufficient for durable rejuvenation. Partial TET-mediated demethylation can reactivate youth genes, yet may also unmask transposable elements, underscoring the need for locus-specific editing rather than global DNMT inhibition.[18]

Histone Modifications and Chromatin/Genome Remodeling

Histones are proteins around which DNA wraps, and post-translational modifications to these proteins further regulate whether genes are active or silent. In youthful skin, enzymes like EZH2[25] and BMI1[26] maintain tissue regeneration by preserving an optimal histone state. These protective enzymes decline with age, leading to diminished regenerative capacity and senescence. Additionally, sirtuins—particularly SIRT1—help control inflammation and prevent DNA damage,[27,28] but they also decrease during aging, promoting pro-inflammatory pathways and matrix degradation.[29,30] Notably, skin aging driven by environmental factors, especially UV radiation, profoundly affects histone modifications: UV exposure increases the activity of enzymes like p300/CBP that add histone acetyl marks, upregulating collagen-degrading enzymes and inflammation.[31]

Beyond histone marks, chromatin gradually loses compaction, exposing normally silenced genes and promoting genomic instability.[32,33] Aging cells also form senescence-associated heterochromatin foci (SAHF) that lock down proliferation genes.[32,34] Although limited in scale, evidence from Hi-C and Micro-C mapping studies in primary fibroblasts[35–37] suggests a decline in enhancer-promoter looping interactions at extracellular matrix (ECM)-associated loci. These findings parallel observations in progeroid models,[37] where disrupted 3D genome architecture coincides with ECM dysregulation and nuclear lamina defects, implying a potential link between spatial genome decay and surface photoaging. Chromatin remodelers like SWI/SNF[38] and LSH/HELLS[39] coordinate these structural shifts, illustrating why wrinkles, laxity, and delayed wound healing represent local injury and genome-wide architectural decay.

MicroRNAs (miRNAs)

Another layer of regulation emerges from microRNAs (miRNAs), small non-coding RNA molecules that fine-tune gene expression. Intrinsic aging typically involves subtle miRNA shifts, such as downregulation of miR-146a, which correlates with reduced collagen production and increased inflammatory signaling.[40,41] By contrast, UV-induced aging (ie, extrinsic aging) triggers more pronounced miRNA dysregulation, rapidly altering numerous pathways involved in DNA repair, apoptosis, and matrix turnover.[42] For instance, UV-induced upregulation of miR-34 and miR-23a promotes senescence and collagen breakdown.[4,43,44] These miRNA changes can intensify damage from environmental exposures, making them attractive therapeutic targets for mitigating extrinsic aging. These miRNA changes often lie downstream of chromatin relaxation and histone-variant exchange, underscoring the multilayered nature of cutaneous epigenetics.

Adding another tier of regulation, longer non-coding RNAs, including long non-coding RNAs (lncRNAs) such as MALAT1 and ANRIL, have been shown to modulate keratinocyte senescence.[45,46] Meanwhile, evidence links circular

RNAs (circRNAs) like circ-COL3A1 to UV-induced loss of extracellular matrix components.[47] Although research in this area is still developing, these findings underscore the increasingly recognized role of diverse non-coding RNAs in the multilayered epigenetic landscape of skin aging.

Environmental Drivers of Epigenetic Aging in Skin

Cutaneous epigenetic drift is highly plastic because the skin sits at the front line of the human exposome: solar radiation, airborne pollutants, tobacco smoke, and lifestyle habits continually deposit molecular scars that accelerate biological age. Unlike intrinsic drift, which accumulates slowly, environmental insults can re-shape the methylome, histone code, chromatin loops, and non-coding RNA networks within hours, leaving durable signatures that translate into wrinkles, laxity, and oncogenic risk (Tables 1 and 2).

Table 1 Epigenetic Changes in the Skin Induced by Environmental Factors

Environmental Factor	Impact	Ref.
UV Radiation	Gene silencing, chromatin relaxation, facilitated DNA repair, apoptosis modulation	[18, 23, 31, 53, 86]
Environmental Pollution	Increased inflammation, oxidative stress, altered gene expression	[48–50,58–60]
Lifestyle and Diet	Preservation of skin health, promotion of inflammation and aging, improved skin homeostasis	[2, 51,77–82]

Table 2 Epigenetic Alterations in Dermatological Diseases

Disease	Epigenetic Mechanism	Details	Impact	Ref.
Skin Cancer	DNA Methylation	Hypermethylation of tumor suppressor gene promoters (eg, CDKN2A)	Promotes uncontrolled cell proliferation and skin cancer development	[6, 83–85]
	Histone Modifications	Increased acetylation of histones H3 and H4	Activates oncogenes	[31, 86–88]
	Non-coding RNAs	Dysregulation of miRNAs and lncRNAs (eg, miR-137 targeting MITF)	Functions as oncogenes or tumor suppressors	[40, 42, 46, 85]
Psoriasis	DNA Methylation	Differential methylation in genes involved in immune response and keratinocyte differentiation	Contributes to hyperproliferation and aberrant differentiation of keratinocytes	[29, 85, 89]
	Histone Modifications	Increased H3K27me3 at IL-10 promoter	Silences anti-inflammatory genes	[29, 30, 85]
	Non-coding RNAs	Upregulation of miR-21	Promotes inflammation	[40, 46, 85]
Atopic Dermatitis	DNA Methylation	Altered DNA methylation in skin barrier function and immune response genes (eg, hypermethylation of FLG)	Leads to impaired skin barrier function	[85, 89, 90]
	Histone Modifications	Decreased H3K9 acetylation in Th2 cytokine genes	Promotes a pro-inflammatory environment	[85, 89, 90]
	Non-coding RNAs	Upregulation of miR-155	Modulates the inflammatory response	[46, 85, 89]

(*Continued*)

Table 2 (Continued).

Disease	Epigenetic Mechanism	Details	Impact	Ref.
Vitiligo and Other Autoimmune Skin Diseases	DNA Methylation	Hypomethylation of TYR gene promoter	Increases antigen presentation and immune-mediated destruction of melanocytes	[24, 85, 89]
	Histone Modifications	Reduced H3K27me3	Overexpresses inflammatory genes	[84, 85, 89]
	Non-coding RNAs	Dysregulation of miR-25 targeting ATG5	Impaired autophagy and immune response	[46, 85, 89]
Aging	DNA Methylation	Global hypomethylation and site-specific hypermethylation	Affects genes involved in skin structure and repair	[4, 8, 9, 11–13, 17, 29]
	Histone Modifications	Reduced H3K9 acetylation and increased H4K16 deacetylation	Reduces expression of genes essential for skin regeneration	[6, 25, 32, 33, 75, 91]
	Non-coding RNAs	Changes in miRNAs and lncRNAs expression (eg, miR-29, miR-34a)	Impacts cellular senescence and extracellular matrix components	[19, 20, 40, 41, 45–47, 52,76,92]

Ultraviolet (UV) Radiation

Ultraviolet (UV) radiation is recognized as the most potent environmental factor driving epigenetic aging in the skin, exerting a distinct effect on photoaging beyond intrinsic chronological processes.[48] Chronic UV exposure induces persistent alterations in the epigenetic landscape, marked by extensive global DNA hypomethylation, in contrast to the more moderate promoter hypermethylation observed with chronological aging.[23,29] This widespread hypomethylation predominantly involves heterochromatic regions and likely arises from UV-induced oxidative damage and depletion of methyl-donor substrates, impairing DNA methyltransferase function.[54] Intriguingly, UV exposure also promotes localized hypermethylation at tumor suppressors and extracellular matrix regulators.[55,83] For example, upregulated DNA methyltransferase 1 (DNMT1) following UV exposure hypermethylates the TIMP2 promoter, reducing its expression and allowing unchecked collagen degradation.[53] This way, focal epigenetic silencing combines with global hypomethylation, creating a dual mechanism directly linking UV-driven epigenetic dysregulation to structural deterioration and heightened oncogenic risk.[53,83]

UV radiation also profoundly alters histone modifications and chromatin structure, collectively reinforcing photoaging pathways.[56,57] Chronic sun exposure increases histone acetylation, often via enhanced histone acetyltransferase (p300) activity and reduced histone deacetylase (HDAC and sirtuin) activity.[31,86,87] These changes correlate with elevated matrix metalloproteinases (eg, MMP1) and pro-inflammatory genes,[61] accelerating collagen breakdown. UV exposure further reduces repressive marks (eg, H3K9 methylation[62]), causing chromatin relaxation and transcriptional activation of inflammation-related and matrix-remodeling genes. Moreover, UV-driven inflammation perpetuates epigenetic modifications through oxidative stress[23,61,89] and cytokine-dependent epigenetic enzyme modulation.[63] Collectively, these UV-induced alterations leave lasting molecular "signatures" on sun-exposed skin, manifesting clinically as accelerated aging and heightened susceptibility to age-related cutaneous disorders.

Pollution and Tobacco Smoke

Pollution and tobacco smoke act similarly to hasten epigenetic aging in the skin, mainly by inducing oxidative stress and inflammation. Particulate matter ($PM_{2.5}$), abundant in urban pollution, triggers DNA methylation shifts through downregulation of DNA methyltransferases (DNMT1/3) and upregulation of TET demethylases,[49] leading to global hypomethylation and activation of senescence genes like CDKN2A (p16INK4A).[50,64] $PM_{2.5}$ thus engages the same DNA methylation pathways implicated in aging, revealing overlapping mechanisms.[65] Concomitant histone modifications—

specifically, the loss of H3K27me3 and gain of H3K4me3—reshape chromatin into a pro-senescence, pro-inflammatory configuration.[50] MicroRNA expression is also perturbed,[58,66] persistently dysregulating inflammation, apoptosis, and stress-response pathways.[67] Ultimately, these changes accelerate collagen degradation and wrinkle formation,[59,60] cementing pollution's role in premature skin aging.

Tobacco smoke compounds similar epigenetic disturbances, including persistent DNA hypomethylation at loci such as AHRR, a well-known biomarker of smoking history.[68,69] This hypomethylation can remain even decades after cessation.[70] Tobacco smoke-induced histone modifications,[88] such as increased histone acetylation at promoters of inflammatory and extracellular matrix-degrading genes,[71] amplify collagen breakdown and chronic inflammation.[70] Smoke exposure also alters microRNA profiles, contributing to sustained dysregulation.[68] Notably, former smokers show elevated epigenetic age acceleration on multiple "clocks," eg, Horvath's EAA, Hannum's EAA, and GrimAge.[72] Collectively, both pollution and tobacco smoke leave lasting epigenetic scars that drive premature skin aging, emphasizing the need for targeted interventions to reduce environmentally induced epigenetic damage.

Other Environmental Contributors

Beyond UV radiation, pollution, and tobacco, various everyday behaviors and exposures likewise imprint lasting epigenetic "scars" on the skin. Diet emerges as a key factor: Mediterranean-style eating patterns rich in antioxidants are linked to more youthful DNA methylation profiles,[77,78] whereas high-sugar diets accelerate epigenetic age.[79] Mechanistically, poor diets evoke oxidative stress and chronic inflammation, promoting stable DNA methylation changes, histone modifications, and altered microRNA expression.[73,80,90] Advanced glycation end-products (AGEs) can further entrench inflammatory states.[80] Conversely, nutrient-rich diets supply critical methyl donors and antioxidants, helping preserve a youthful epigenetic landscape.

Alcohol consumption, psychological stress, insufficient sleep, sedentarism, and endocrine-disrupting chemicals (EDCs) also leave cumulative epigenetic marks that hasten skin aging. Chronic alcohol intake accelerates epigenetic age by about 2.22 years.[74] Prolonged psychological stress activates glucocorticoid receptors,[93] driving methylation changes at stress-responsive genes like FKBP5 and impairing skin regeneration.[94,95] Disrupted sleep and circadian rhythms similarly foster aberrant methylation of clock and repair genes,[96,97] eroding the skin's capacity for timely repair.[98] Physical inactivity further promotes pro-inflammatory shifts, whereas regular exercise reduces DNA methylation age acceleration, partly via beneficial microRNA modifications.[51,81,82] Lastly, EDCs in plastics, cosmetics, and pesticides subtly but persistently alter the skin's epigenome and immune function.[99] Collectively, these factors highlight how lifestyle choices and daily exposures can intensify or alleviate the molecular imprint of aging on the skin.

Current Clinical Interventions and Epigenetic Effects in the Skin

Although the environmental and lifestyle factors discussed can accelerate skin aging via epigenetic dysregulation, emerging therapies suggest that targeted interventions may improve clinical outcomes and reshape the skin's epigenetic landscape. (Table 3) This section examines conventional anti-aging interventions, newer epigenome-targeted approaches, and senescence-modulating drugs.

Conventional Anti-Aging Therapies

Conventional anti-aging interventions, such as retinoids, alpha-hydroxy acids (AHAs), and dermatologic laser resurfacing, are widely used to improve visible signs of skin aging by stimulating collagen synthesis, accelerating epidermal turnover, and supporting fibroblast activity.

Topical Retinoids

Retinoids (eg, tretinoin, retinol) enhance skin texture by activating retinoic acid receptors, increasing collagen, and inhibiting matrix metalloproteinases.[100] Recent studies also hint at a link between retinoid pathways and DNA methylation. For instance, restoring TET2 activity can reverse hypermethylation of the RARβ promoter, enhancing tumor cell sensitivity to retinoic acid in cutaneous squamous cell carcinoma.[101] Moreover, RAR activation dissociates co-repressor complexes (including HDACs), thereby increasing histone acetylation and opening chromatin.[102] Although these findings imply retinoids may modulate DNA methylation in photoaged or diseased skin, their direct impact on healthy human skin

Table 3 Epigenetic-Targeted and Conventional Interventions with Documented Rejuvenating Effects in Human Skin

Intervention Category	Representative Agent/Modality	Primary Epigenetic Target(s)	Key Evidence (Mo Level)	Main Clinical Outcomes	Ref.
Conventional topical actives	Tretinoin, retinol	↑ histone acetylation via RAR-co-activator exchange; context-dependent promoter demethylation (eg, RARβ)	Keratinocyte & fibroblast cultures; small RCTs in photo-aged skin	↓ fine wrinkles, ↑ collagen I, smoother texture	[100–104]
	Glycolic acid 5–20% (α-hydroxy acid)	Promoter hyper-/ hypomethylation (↓ NLRC4, AIM2); MAPK-linked histone shifts	Keratinocytes; split-face trials	Improved hydration, ↑ procollagen, ↓ erythema	[105–109]
	Fractional CO_2, Er: YAG lasers	Global DNA-methylation "clock" rollback; ↑ H3/H4 acetylation; miRNA reset	Human ex-vivo skin; prospective clinical studies	↓ wrinkle depth, ↑ dermal density, faster barrier recovery	[110–115]
Epigenome-targeted agents	Dihydromyricetin (DNMT1 inhibitor)	Partial reversal of age-related CpG hypermethylation	Primary keratinocytes; pilot cosmetic study (n = 43)	–2 yr DNAm age; –78% wrinkle volume (4 wk)	[84, 116–118]
	Resveratrol (broad HDAC / SIRT1 modulator)	Restores HDAC2/7, ↑ SIRT1 → chromatin tightening	Mouse & human explants; topical RCTs	↑ elasticity, ↓ roughness, ↑ antioxidant gene expression	[119–121]
	HDAC6-selective inhibitors (eg, tubacin, ACY-1215)	Tubulin de-acetylation → ↓ IL-1β secretion	Diabetic-wound mice; pre-clinical	Accelerated closure, improved angiogenesis	[122, 123]
Senescence-directed approaches	Dasatinib + quercetin; fisetin (senolytics)	Apoptosis of p16INK4a-high cells; SASP reduction	UV- / D-gal models; early human trials pending	↓ MMPs, ↓ inflammation; smoother dermis in mice	[91, 124, 125]
	Rapamycin cream 0.1% (senomorphic)	mTOR inhibition → ↓ p16INK4a, ↑ collagen VII	Double-blind split-face RCT (24 wk)	↓ rhytides, ↑ dermal-epidermal junction integrity	[126]
	OS-01 peptide / Pep-14	NRF2-HDAC axis → SASP suppression, DNAm-age rollback	Ex-vivo aged skin; Phase I study under review	–1.5 yr DNAm age; ↑ barrier gene expression	[92]

Notes: ↑: Increased; ↓: Decreased; → Leading to.

remains unclear.[14] Most investigations have focused on retinoid-related gene methylation in pathological contexts, highlighting a need for more research on direct retinoid-induced epigenetic shifts.[103,104]

Alpha-Hydroxy Acids

Similarly, alpha-hydroxy acids (eg, glycolic acid, GA) rejuvenate skin primarily through controlled exfoliation and fibroblast activation, boosting collagen production and improving structural integrity.[105] Beyond these effects, GA also displays epigenetic properties, influencing DNA methylation to modulate gene expression. Notably, a 2016 study showed that GA hypermethylates and silences pro-inflammatory genes such as NLRC4, AIM2, and ASC in keratinocytes.[106,107] As a result, inflammatory pathways are repressed, promoting a less inflamed, more youthful phenotype. GA additionally upregulates collagen and hyaluronic acid gene expression in skin biopsies,[108] suppresses UVB-induced MMP-9 activity,

and restores aquaporin-3 and collagen levels through epigenetic and MAPK-mediated pathways.[109] GA may support a more youthful skin gene-expression profile by modulating key epigenetic regulators. However, further in vivo research is needed to clarify whether these epigenetic shifts lead to lasting clinical gains.

Laser Resurfacing

Laser resurfacing (ablative and non-ablative, including fractional CO_2 and erbium:YAG) is another standard modality that harnesses wound-healing processes to replace aged skin with new tissue.[110] Earlier research concentrated on surface enhancements—reducing wrinkle depth and boosting elasticity—yet more recent studies show that laser treatments can also epigenetically reprogram the skin.[15,111,112] Observed changes include DNA methylation reversion, histone acetylation, and shifts in non-coding RNA expression.[113,114] Laser resurfacing can reset certain epigenetic clocks, reflecting a biological rejuvenation that extends beyond visible outcomes.[115] MicroRNA changes post-laser also contribute to anti-inflammatory and antifibrotic effects, fostering orderly tissue remodeling.[111] This involves chromatin remodeling, notably increased histone acetylation and promoter demethylation of crucial extracellular matrix genes.[111,113] Moreover, combining laser therapy with topical agents such as vismodegib can further modify early carcinogenic lesions, suggesting a synergistic, epigenetically driven boost in therapeutic effectiveness.[127] Thus, laser-based approaches appear capable of epigenetic reprogramming, offering an opportunity for a more precise anti-aging regimen.

Epigenome-Targeted Approaches

Beyond conventional methods, epigenome-targeted interventions aim to correct age-related epigenetic "errors" at their source. DNA methyltransferase (DNMT) inhibitors have gained attention for their potential to demethylate silenced, youth-associated genes without inducing genomic instability.[116] In aged skin cells, global hypomethylation coexists with local hypermethylation of vital regenerative genes.[20,84] By partially inhibiting DNMT activity, researchers attempt to reverse this imbalance, reactivating genes crucial for maintaining a youthful phenotype. Dihydromyricetin (DHM), which is a flavonoid discovered via natural compound screening, directly inhibits DNMT1, shifting thousands of methylation sites toward a "younger" pattern in keratinocytes and restoring multiple "youth genes".[117] Intriguingly, DHM treatment has been shown to reduce the epigenetic age of treated cells by about two years and lower a "wrinkle prediction" score by nearly four years.[117] A small clinical study (n=43) reported a 78% reduction in wrinkle volume after four weeks.[118] Together, these findings suggest DHM-based DNMT inhibition may counteract epigenetic aging processes rooted in environmental insults, delivering both molecular and clinical youthfulness.

Histone deacetylase (HDAC) inhibition represents another strategy. In aged skin, loss of HDACs contributes to epigenetic drift—characterized by increased histone acetylation, "silencing" of youth-associated genes, and inflammation.[87,119] Compounds targeting HDACs can restore protective gene expression (eg, antioxidant enzymes, structural proteins) while repressing harmful factors like MMPs and cytokines.[120] Early human trials using topical HDAC inhibitors (eg, resveratrol) demonstrate improved elasticity, smoothness, and overall appearance, reinforcing the concept of "epigenetic skincare".[121] Preclinical models further show that HDAC modulation accelerates wound closure, encourages angiogenesis, and fosters a regenerative immune environment.[122] By remodeling chromatin, HDAC inhibitors enhance cell proliferation/migration and facilitate a pro-healing macrophage phenotype. Emerging selective approaches (eg, HDAC6 inhibition in diabetic wounds[123] or dual HDAC/LSD1 inhibition for keratinocyte migration)[128] exemplify the precise tailoring possible with epigenetic therapies.

Senescence-Targeting Drugs

Because senescent cells accumulate with age and drive chronic inflammation, matrix degradation, and reduced tissue repair via the senescence-associated secretory phenotype (SASP),[91,124] pharmacologically targeting these cells has become a pivotal approach. Senolytics selectively remove senescent cells by exploiting markers like high p16INK4a and p21Cip1/Waf1. Agents such as dasatinib + quercetin and fisetin have demonstrated the ability to reduce pro-inflammatory and matrix-degrading mediators, leading to diminished collagen breakdown and wrinkle formation.[91,125] Meanwhile, senomorphics (eg, rapamycin, OS-01 peptide/Pep14) dampen the harmful SASP without killing the cells, improving DNA repair and preserving overall tissue integrity. Topical rapamycin, for instance, significantly lowered p16INK4a and boosted dermal collagen VII, correlating with fewer wrinkles and a more robust barrier.[126,129] Likewise,

OS-01 applied to ex vivo aged human skin reduced p16INK4a, reversed SASP-related gene signatures, and partially reset DNA methylation age.[92] These outcomes imply that directly targeting senescent cells or their secretory profiles may realign the epigenetic clock and slow, or even partially reverse, the aging trajectory of the skin.

Discussion

Despite the rapid growth of epigenetic research in dermatology, critical questions remain regarding the precise drivers of epigenetic aging, how best to measure it, and how to translate these findings into clinically viable interventions. Recent work reveals that aging skin accumulates aberrant DNA hypermethylation, perturbing genes involved in matrix organization and metabolic balance.[15] Still, unresolved debates persist about whether these epigenetic changes or somatic mutations take precedence as primary aging drivers.[76] Crucially, the idea that epigenetic alterations are merely correlative is increasingly challenged: a 2023 Epigenome-Wide Mendelian Randomization analysis identified 1299 CpG sites causally influencing perceived facial aging,[7] while experimental interventions continue to reinforce the functional role of these changes.

Although epigenetic modifications in aging skin are recognized as functionally necessary, there remains uncertainty about their long-term dynamics and causal mechanisms. Most published data are still derived from cross-sectional analyses, which cannot capture the fluidity of epigenetic changes over time. Indeed, a 2023 study tracking 64 individuals for 15 years discovered that most age-associated methylation markers did not follow uniform trajectories, highlighting considerable inter-individual variability and emphasizing the need for longitudinal cohort studies with repeated sampling.[52] Such variability complicates the development of robust epigenetic clocks or one-size-fits-all interventions.

Another challenge arises from the cellular heterogeneity of skin, including fibroblast subtypes, Langerhans cells, and other specialized populations whose epigenetic signatures can diverge more by developmental origin than by shared environment.[130–133] Bulk tissue profiling can overlook critical cell-type-specific phenomena, such as selective basal stem cell reprogramming in certain inflammatory skin diseases.[133] High-resolution, cell-specific epigenomic approaches are thus vital for unraveling local lineage diversity and the mosaic of epigenetic aging within different skin compartments.

Although research on epigenetic interventions (DNMT, HDAC, SIRT modulators, etc.) is advancing rapidly, relatively few rigorous clinical trials have tested these agents specifically for skin aging.[85] Overall, many compounds for medical applications with a epigenetic mode of action remain in early-phase evaluation, and regulatory timelines for approval are unclear. Targeted drug delivery also poses substantial hurdles: while the skin's barrier functions protect against environmental insults, they can impede penetration of topically applied agents, raising concerns about off-target availability and systemic toxicity.[134] Innovations such as nanomedicine-based formulations and other advanced delivery platforms promise to boost local bioavailability while mitigating adverse effects.[75]

Emerging data indicate that epigenetic aging trajectories differ by sex, ethnicity, geography, and even local microbiome composition.[135,136] Hormonal variations, genetic background, diet, hygiene practices, and unique microbial ecosystems shape an individual's epigenome.[136] Some skin conditions frequently seen in Western settings appear rare in non-Westernized communities, hinting at microbiome-mediated epigenetic protection.[137] Integrative "multi-omics" strategies encompassing metagenomics, metabolomics, and epigenomics are needed to clarify how microbial metabolites and environmental factors regulate chromatin states across diverse populations.[135,138]

Conclusion

Epigenetic research in human skin aging stands on the precipice of significant breakthroughs but requires overcoming critical hurdles outlined here: mechanistic uncertainties, translational barriers, and challenges posed by sociodemographic variability. Future progress hinges on integrating longitudinal, cell-specific, and ethnically diverse datasets, refining targeted epigenetic therapies through advanced drug delivery systems, and gaining a comprehensive understanding of microbiome-epigenome interactions. By addressing these multifaceted gaps, the field can advance beyond correlations to achieve meaningful, precision-driven clinical outcomes, ultimately redefining therapeutic strategies for age-related skin conditions as well as cosmetic product applications.

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