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Unique synergistic combination of biomimetic DNA and catalytic environment to improve and go beyond cell longevity, proven by Proteomics.

Sophie VANN-GUILLON [1], Laura NUCIBELLA [2], Anneleen LAVIGNE [3], Clara CHARLOT[3], Marie LE CORRE[3]

[1]CEO, [2]Research & Development Deputy Director, [3]Research and Development Project Managers, CVL COSMETICS SA, VALMONT GROUP, 1 place du port, 1110 Morges, Switzerland

The use of deoxyribonucleic acid (DNA), in esthetic medicine, is known to have beneficial effects on skin regeneration. However, in cosmetics, its performance and efficacy are often limited by its quality and formulation that influences its mode of action. For the first time, the efficacy of DNA was evaluated in association with various molecules, in a proteomic study on the expression profile of 3557 proteins, aiming to positively impact key keratinocyte pathways involved in proliferation and differentiation.

Using this method, the objective was to demonstrate that a unique combination of a specific DNA with a selected natural environment was able to improve keratinocyte regeneration, vitality, longevity and protection.

In the first step, a naturally sourced DNA was evaluated alongside a different evolution of a Silicon-derived DNA (DNA-S) known to be modulated by environmental factors. In the second step, a specific natural formulation medium rich in micronutrients was selected and used as a catalytic environment to modulate DNA-S for optimized efficacy (DNA-SE).

Proteomic analysis revealed no significant effects on the energetic cell metabolism with DNA, while DNA-S enhanced it by 54%, primarily through a 40% increase in TCA cycle activity. In contrast, DNA-SE significantly amplified cellular metabolic activity, doubling overall energy metabolism (+100%). This was achieved through a 32% increase in TCA cycle activity, a 28% enhancement in ATP production, and a 40% stimulation of mitochondrial Complex I biogenesis. These improvements contributed to enhance mitochondrial functionality and MEC synthesis (+39%), showing the synergistic capability of the catalytic environment. Regeneration pathways showed comparable effect on mitosis and autophagy but DNA-S enriched desmosome components (+80%), while DNA-SE promoted DNA repair processes (+42%). Skin barrier function was reinforced by 51% with DNA, by 47% with DNA-S, and 113% with DNA-SE, demonstrating the synergistic potential of the catalytic environment.

Compared to pure DNA and DNA-S, the DNA-SE complex showed a unique symbiotic anti-aging effect, acting not only on cell longevity by improving the cell energy and vitality but also strongly reinforcing the skin barrier function and protection, highlighting the influence of

the natural environment on DNA-S's efficacy. These positive results are confirmed in in-vivo studies.

Keywords: Anti-aging, Barrier function, Ingredients combination, Omics, Regenerative beauty

1. Introduction

Skin longevity is a major focus in dermatological and cosmetic research, as aging is a complex and multifactorial process driven by both intrinsic and extrinsic factors [1]. It is associated with a progressive decline in biological functions, caused by the accumulation of molecular, cellular, and systemic alterations —a framework defined by the 12 hallmarks of aging [2]. Among these, mitochondrial dysfunction disrupts metabolic efficiency, leading to reduced ATP production and energy availability [3]. This decline contributes to cellular impairments, weakening regenerative capacity and ultimately compromising skin homeostasis and vitality. Clinically, these biological alterations translate into increased skin fragility, fine lines, wrinkles, and pigmentation irregularities, alongside a progressive loss of elasticity and firmness. Additionally, the decline in metabolic activity and cellular energy slows down regenerative processes and compromises the skin barrier, further amplifying visible signs of aging such as dryness and a dull complexion [4].

Skin vitality and longevity are intrinsically connected, as vitality reflects the skin's internal metabolic efficiency, which sustains its health, resilience, and ability to adapt to external stressors. A metabolically active skin maintains optimal oxygenation, hydration, and renewal processes, ensuring smoothness, suppleness, and elasticity for a plumped and firm appearance. Additionally, a reinforced skin barrier enhances protection against environmental aggressors, preserving structural integrity and functional balance. By maintaining these dynamic processes, the skin is better equipped to counteract the effects of aging and sustain its long-term health.

Aging-related declines in metabolic efficiency, regenerative potential, and environmental resilience have driven growing interest in bioactive molecules that support skin homeostasis and longevity. Among these, deoxyribonucleic acid (DNA) has emerged as a key candidate due to its multifunctional properties extending beyond its genetic role. As a macromolecule, DNA plays a crucial role in cellular metabolism, tissue repair and skin regeneration.

However, despite their intrinsic biological potential, the use of DNA-based ingredients in cosmetics remains constrained by critical formulation challenges, including stability, bioavailability, and limited penetration through the stratum corneum, which acts as a major barrier for high-molecular-weight biomolecules and ultimately reduces their efficacy [5]. To overcome these limitations, a biomolecular hybrid composed of DNA and silicon—termed DNA-S—has been engineered to enhance both regenerative and structural performance. DNA is well recognized for its role in cellular repair and renewal, while silicon contributes to extracellular matrix organization and collagen synthesis [6]. This molecular synergy not only preserves the functional stability of both components but also optimizes their bioavailability and biological activity, thereby supporting skin homeostasis and regeneration.

Moreover, DNA-S remains highly sensitive to environmental conditions, which influences its stability and interactions with cellular components. To further optimize its performance, DNA-S has been integrated into a biochemical environment (DNA-SE) designed to modulate its structure and maximize its bioavailability. This selected natural environment, compared to a biomimetic system, fine-tunes specific conditions to modulate molecular conformation and overall efficacy, thus potentiating its beneficial effects on skin regeneration, structuration and protection. By addressing key challenges related to molecular stability and bioactivity through

molecular synergy and environmental modulation, this approach represents a significant advancement in the development of next-generation pro-longevity bioactive technologies.

This study explores the potential of DNA-based active ingredients by assessing the impact of a medium enriched with a specific natural formulation (DNA-SE) on silicon-derived DNA (DNA-S). Specifically, it examines how a catalyzing environment potentiates the bioactivity of this dynamic DNA-silicon complex. To achieve this, a comprehensive proteomic analysis was conducted on keratinocytes, essential regulators of epidermal homeostasis and skin barrier function. For the first time, an exhaustive dataset of 3,557 proteins was analyzed to provide in-depth insights into the molecular mechanisms influenced by silicon-derived DNA and its biomimetic environment. By comparing DNA, DNA-S, and DNA-SE to untreated cells, this study examines whether the environmental modifications enhance the biological potential of DNA-S. The findings highlight distinct protein expression patterns associated with the silicon presence and the biomimetic environment, suggesting a synergistic effect that modulates key biological pathways involved in skin regeneration, vitality, and longevity.

2. Materials and Methods

2.1. Characterization of DNA-based active ingredients:

Three different DNA-based active ingredients were tested in this study: a naturally sourced DNA (DNA), a silicon-derived DNA (DNA-S), and DNA-S formulated in a specific catalytic environment (DNA-SE).

- Naturally sourced DNA (DNA) is a polynucleotide that serves as the reference in this study, representing unmodified DNA.
- Silicon-derived DNA (DNA-S) is a derived form of DNA.
- Biochemically enriched DNA-S (DNA-SE) combines DNA-S with a natural specific enriched environment. This formulation was designed to modulate DNA-S bioactivity by influencing its molecular conformation and improving its bioavailability.

All DNA-based active ingredients were tested at predetermined concentrations. Their cytotoxicity was evaluated through cell viability assays to determine an effective and non-toxic working concentration, ensuring optimal conditions for subsequent proteomic analysis.

2.2. Keratinocyte cell culture and treatment:

Normal human epidermal keratinocytes (NHEKs) from a single donor (Promocell) were cultured and maintained as monolayers at less than 75% confluence in the Promocell-recommended culture medium. The cells were incubated at 37°C in a humidified atmosphere containing 5% CO_2. For passaging, NHEKs were detached using a combination of purified trypsin and trypsin inhibitors/BSA and were used up to passage 6. The tested DNA-based active ingredients (DNA, DNA-S, and DNA-SE) were serially diluted in culture medium at predetermined concentrations and filtered through a 0.2 µm membrane to maintain sterility. The solutions were applied to NHEK cultures for 48 hours under standardized conditions. Each condition was tested in triplicate within a single experimental run, using an untreated reference control. To ensure data reproducibility, all treatments were performed under sterile conditions in a controlled cell culture environment.

2.3. Protein extraction and quantification:

Protein extraction was performed on treated keratinocytes using the Minute™ Total Protein Extraction Kit for Skin Tissue (Interchim). After lysis, samples were centrifuged to remove cellular debris, and supernatants containing soluble proteins were collected and stored at -80°C until further analysis. Protein concentrations were determined using the Pierce™ BCA

Protein Assay Kit (Fisher Scientific). A BSA standard curve was generated to ensure accurate quantification, with absorbance readings measured at 562 nm using a Cytation 5 Cell Imaging Multi-Mode Reader (BioTek). Protein extracts were then normalized to 1 µg/µL using extraction buffer (Interchim) and 1X Laemmli buffer (Bio-Rad) supplemented with 5% β-mercaptoethanol. Samples were subsequently denatured before analysis by SDS-PAGE and mass spectrometry.

2.4. LC-MS/MS analysis:

Proteins were separated by SDS-PAGE, digested into peptides, and analyzed using a LTQ Orbitrap Fusion LUMOS mass spectrometer (Thermo Fisher) with a 146-minute gradient optimized for high-resolution peptide separation. The acquired MS/MS spectra were processed using Proteome Discoverer (version 2.5) and searched against the *Homo sapiens* proteome (UP000005640, 20,371 reviewed entries).

Database searches were conducted with monoisotopic mass selection, using trypsin as the cleavage enzyme, allowing up to two missed cleavages. Carbamidomethylation of cysteine was set as a fixed modification, while N-terminal acetylation and methionine oxidation were considered variable modifications. Identifications were filtered based on a false discovery rate (FDR) threshold, ensuring high-confidence protein detection. Sample quality was systematically assessed before further analysis.

The Proteome Discoverer workflow ensured quality control and data integrity, allowing reliable protein identification and quantification for downstream biological interpretation.

2.5. Bioinformatics analysis:

Proteomic analysis identified 3,557 quantifiable proteins, with 3,283 consistently detected and annotated across all conditions. Proteins exhibiting a twofold increase or decrease in abundance relative to the untreated control were considered significantly regulated, based on statistical thresholds applied during data processing, and selected for further investigation.

To determine the biological significance of these changes, differentially expressed proteins and their interacting partners were categorized based on their biological processes, molecular functions, and pathway associations. A bioinformatics pipeline integrating protein database searches, interaction network mapping, and functional annotation was applied to extract relevant biological insights.

The processed data were further analyzed to explore cellular pathways and molecular mechanisms, focusing on how DNA-based treatments influence keratinocyte function and epidermal homeostasis. The detailed statistical analysis of protein expression changes was conducted separately.

2.6. Statistical analysis:

Protein quantification data were normalized and log-transformed to ensure comparability across samples. A two-way ANOVA was performed to assess global variations in protein expression, assuming that most proteins remain stable under experimental conditions, and to evaluate potential interactions between treatment factors. Tukey's multiple comparison test was applied post hoc to identify significant pairwise differences between conditions.

A false discovery rate (FDR) correction was used to control for multiple comparisons, with a significance threshold of $p < 0.05$. Statistical computations were performed using GraphPad Prism 9. The resulting statistical insights were integrated into the biological interpretation of protein expression changes.

3. Results

3.1. Comprehensive proteomic analysis reveals the molecular impact of DNA-based treatments

To evaluate the effect of the biochemical environment on the molecular activity of DNA-based active ingredients, normal human epidermal keratinocytes (NHEKs) were treated with equivalent non-cytotoxic concentrations of DNA in the form of DNA, DNA-S, or DNA-SE, as determined through cytotoxicity assays, or left untreated as a control. After 48 hours, a quantitative proteomic analysis was performed using LC-MS/MS. A total of 3,557 proteins were identified and quantified across all experimental conditions, of which 3,283 were consistently detected in all samples and retained for further analysis.

3.2. DNA-SE induces the highest number of differentially expressed proteins

Proteins exhibiting a fold change (FC) ≥ 2 or ≤ 0.5 with a statistical significance of $p < 0.05$ relative to the untreated control were considered differentially expressed. Among these, 201 proteins were significantly modulated by DNA, 299 by DNA-S, and 343 by DNA-SE, showing the progressive enhancement of molecular effects with the silicon form and, most notably, with the catalytic biochemical environment (*Table I*). This trend highlights the pivotal role of the biomimetic environment (DNA-SE) in amplifying and harmonizing qualitatively and quantitatively the biological response. Functional enrichment analysis of differentially expressed proteins revealed that the catalytic environment (DNA-SE) potentiated key biological pathways, suggesting a synergistic effect that reinforces the metabolic and structural integrity of the skin.

Table I. Number of differentially expressed proteins across conditions.

Differential expression was defined as a fold change (FC) ≥ 2 (upregulated proteins) or ≤ 0.5 (downregulated proteins) with a statistical significance of $p \leq 0.05$ relative to untreated keratinocytes. The number of upregulated and downregulated proteins is reported for each treatment condition.

Condition	Upregulated proteins	Downregulated proteins	Total differentially expressed proteins
DNA	99	102	201
DNA-S	151	148	299
DNA-SE	167	176	343

To better understand the biological significance of these molecular modulations, a pathway-level analysis was conducted to identify the specific cellular processes most impacted by each DNA-based active ingredient. This functional categorization revealed key pathways involved in energy metabolism, cellular regeneration, and barrier formation/protection. The following sections present a detailed exploration of these enriched pathways, highlighting the progressive and synergistic effects the silicon form and of the biochemical environment on keratinocyte function.

3.3. Enrichment of cellular energy metabolism pathways

Proteomic analysis revealed no significant enrichment of metabolic pathways following treatment with DNA. Protein abundance changes related to cellular energy metabolism remained minimal, with non-significant variations observed in TCA cycle proteins (+12% *vs* untreated) and cellular respiration proteins (+6% *vs* untreated) compared to untreated keratinocytes (NT). These findings suggest that DNA alone does not substantially influence keratinocyte energy metabolism.

In contrast, DNA-S treatment triggered a pronounced upregulation of energy metabolism-

related pathways, with 54% of regulated proteins linked to mitochondrial function, including a 40% increase ($p \leq 0.05$ *vs* untreated) of TCA cycle components. This may indicate an enhancement in keratinocyte bioenergetics.

The most pronounced effects were observed with DNA-SE, which strongly enriched cellular energy metabolism pathways. TCA cycle protein levels increased by 32% ($p \leq 0.05$ *vs* untreated), and proteins of the mitochondrial respiratory chain—essential for ATP production—were also upregulated (+28%, $p \leq 0.05$ *vs* untreated). In addition, Complex I biogenesis was enhanced by 40%, suggesting improved electron transport efficiency. Taken together, these cumulative effects led to a 100% increase in overall metabolic activity compared to untreated keratinocytes. This enhanced mitochondrial functionality was further associated with a 39% increase in MEC synthesis (data not shown), highlighting the synergistic power of the catalytic environment provided by DNA-SE.

These results indicate a progressive enhancement of keratinocyte metabolism, with minimal effects from DNA, metabolic activation by DNA-S, and synergistic reinforcement of mitochondrial function and bioenergetics by DNA-SE. This supports the hypothesis that the hybrid molecule and the specific micronutrient-enriched environment act synergistically to optimize cellular energy metabolism. Specifically, the increased Complex I biogenesis, TCA cycle activity, and cellular respiration suggest a sustained ATP production, which is essential for proliferation, repair, and overall skin homeostasis. By preserving cellular energy balance, these mechanisms may contribute to enhanced skin vitality and longevity.

3.4. Enrichment of cellular regeneration pathways

The proteomic analysis revealed no significant enrichment of pathways related to cellular regeneration following treatment with DNA. Protein abundance changes remained minimal, with a decrease in DNA repair proteins compared to the untreated control (NT). These findings suggest that DNA does not substantially impact keratinocyte regenerative mechanisms.

DNA-S upregulated proteins involved in mitosis (+15%, $p \leq 0.05$ *vs* untreated), suggesting an improvement in cellular turnover. Furthermore, autophagy-related proteins were upregulated by +15% ($p \leq 0.05$ *vs* untreated), suggesting a potential role in maintaining cellular recycling processes. These findings suggest a promotion of key mechanisms involved in epidermal renewal and integrity.

DNA-SE exhibited the most notable enrichment of multiple regeneration-associated pathways. DNA repair proteins were upregulated by +42% ($p \leq 0.05$ *vs* untreated), suggesting enhanced genomic stability and cellular stress resistance. Furthermore, signalling pathways related to cellular communication, proliferation, migration and differentiation, including Eph-Ephrin signalling, were upregulated by +22% ($p \leq 0.05$ *vs* untreated) [8]. While mitotic activity showed a slight increase (+9% *vs* untreated), this change was not statistically significant.

These results indicate a progressive enhancement of keratinocyte regeneration, with DNA having minimal effects, DNA-S promoting cell proliferation and autophagy, and DNA-SE reinforcing DNA repair, autophagy, and cellular communication pathways. This supports the hypothesis that silicon form and the catalytic environment act synergistically to optimize epidermal renewal. By enhancing proliferation, autophagy, and genomic maintenance, these modifications may contribute to improved regenerative capacity.

3.5. Enrichment of skin barrier formation and antioxidant protection pathways

The proteomic analysis revealed a moderate enrichment of pathways related to skin barrier formation and oxidative stress response following treatment with DNA. While proteins involved in cornified envelope formation were upregulated (+51%, $p \leq 0.05$ *vs* untreated), indicating a stimulation of keratinocyte terminal differentiation, the modulation of antioxidant-related

proteins remained modest, with glutathione metabolism proteins increasing by only +35% ($p \leq 0.05$ *vs* untreated). These results suggest that DNA exerts limited effects on epidermal protection and structural integrity.

In contrast, silicon-derived DNA (DNA-S) induced a stronger modulation of these protective pathways. Desmosomal proteins, essential for intercellular cohesion and barrier function, were significantly upregulated (+80%, $p \leq 0.05$ *vs* untreated), supporting the mechanical integrity of the epidermis.

DNA-SE treatment resulted in the most robust activation of protective pathways. Cornified envelope proteins were significantly enriched (+113%, $p \leq 0.05$ *vs* untreated), suggesting an optimized process of epidermal differentiation and barrier formation. In parallel, glutathione-related proteins were strongly upregulated (+120%, $p \leq 0.05$ *vs* untreated), pointing to enhanced antioxidant capacity and redox homeostasis. While the increase in desmosomal proteins remained moderate (+16% *vs* untreated), this still supports improved epidermal cohesion and communication.

Overall, these findings indicate a progressive enhancement of skin barrier integrity and antioxidant defense, with DNA exerting moderate effects, DNA-S promoting differentiation and redox balance, and DNA-SE significantly reinforcing these protective mechanisms. This finding supports the hypothesis that the hybrid molecule, in combination with the catalytic environment, enhances beneficial effects on epidermal resilience and long-term skin homeostasis, ultimately promoting skin longevity.

4. Discussion

This study marks a significant milestone as the first to investigate a strategy combining silicon-derived DNA with a highly selected biochemical environment to potentiate its bioavailability and biological activity in skin cells. While DNA has long been recognized for its regenerative and reparative properties in dermatology and aesthetic medicine, its topical cosmetic applications remain limited by poor bioavailability [5].

In this approach, specifics DNA and silicon, known for their roles in supporting cellular regeneration and in structuring the extracellular matrix and promoting collagen synthesis [7], were formulated into a natural medium enriched environment (DNA-SE), specifically designed to mimic physiological conditions and synergistically enhance the stability and activity of both components. This biomimetic context is hypothesized to act as a catalytic system, facilitating optimal molecular interactions and amplifying downstream biological effects. To our knowledge, this is the first proteomics-based investigation to systematically compare the molecular responses elicited by DNA, DNA-S, and DNA-SE in human keratinocytes, offering unprecedented insights into how modulating the biochemical environment can unlock the full regenerative, metabolic, and protective potential of DNA-based actives to support skin vitality and longevity.

The inclusion of DNA-S within a defined biochemical environment (DNA-SE) emerged as a decisive factor in enhancing mitochondrial function by targeting fundamental bioenergetic pathways. Mitochondrial dysfunction is widely recognized as an early and central hallmark of cellular aging, impairing ATP production and consequently affecting all cellular mechanisms dependent on this energy [2-4]. The observed amplification of Complex I biogenesis with DNA-SE suggests a significant improvement in mitochondrial electron transport efficiency, addressing the root cause of metabolic decline.

Beyond Complex I, the biochemical environment also triggered a broad metabolic reprogramming, notably through a strong upregulation of the tricarboxylic acid (TCA) cycle and cellular respiration pathways, two essential processes for maintaining cellular energy homeostasis. This metabolic activation enhances mitochondrial efficiency and supports sustained ATP production, which is critical to meet the high energy demands of epidermal regeneration, the establishment of a functional barrier, and protection against environmental stressors. Importantly, the micronutrient-enriched environment not only acts upstream by improving mitochondrial function and Complex I biogenesis, but also downstream by amplifying energy-dependent biological processes such as DNA repair, autophagy, and mitotic activity. This dual modulation reinforces the skin's capacity for renewal and maintenance, positioning DNA-SE as a comprehensive bioactive strategy for supporting cutaneous vitality and resilience and finally skin health.

The observed metabolic remodeling induced by the biochemical environment not only fuels key regenerative pathways but also creates favorable bioenergetic conditions for terminal keratinocyte differentiation and the formation of a functional epidermal barrier. While aging is characterized by an age-related glycolytic shift [9], these findings align with the fundamental role of mitochondria in the dynamic regulation of stem cell fate and epidermal differentiation. In healthy skin, the metabolic transition from glycolysis in proliferative basal keratinocytes to oxidative phosphorylation in differentiating suprabasal cells is crucial for barrier formation [10,11]. This metabolic switch ensures sustained ATP production, supporting keratinocyte maturation, cornified envelope formation, and epidermal barrier integrity. As mitochondrial function declines with age, these energy-dependent processes become progressively impaired, a phenomenon further exacerbated by external stressors collectively defined as the skin aging exposome [1]. By simultaneously restoring mitochondrial function, activating metabolic circuits, and reinforcing epidermal regeneration and differentiation, DNA-SE addresses multiple biological layers of skin aging. This multi-targeted approach appears particularly relevant to promote long-term skin vitality and resilience.

In addition to these molecular effects, topical application of the micronutrient-enriched environment significantly improved the bioavailability of silicon-derived DNA (DNA-S), as demonstrated by dedicated skin penetration studies (data not shown). The enhanced transcutaneous diffusion observed with DNA-SE supports the hypothesis that environmental modulation not only stabilizes the active complex but also facilitates its sustained interaction with epidermal cells. This improved delivery profile likely contributes to the broader biological effects observed *in vitro*.

These findings are further supported by complementary clinical investigations, conducted in parallel, assessing the topical application of the DNA-SE formulation on human skin. Preliminary results indicate a measurable improvement in key parameters of skin vitality and structure, hydration, radiance, firmness, and epidermal thickness, bringing them closer to the profile of youthful, healthy skin. While detailed clinical outcomes will be reported separately, they provide converging evidence that the biochemical environment plays a decisive role in potentiating the *in vivo* performance of DNA-based actives.

5. Conclusion

Together, these results position DNA-SE as a promising biomimetic technology capable of restoring core biological functions in aging skin. By targeting key cellular pathways—from mitochondrial activity to epidermal regeneration and defense mechanisms—the micronutrient-enriched environment acts across multiple hallmarks of skin aging (*Figure 1*).

Far from acting independently, these biological processes are tightly interconnected. Enhanced energy metabolism supports not only regeneration and repair but also the systems responsible for maintaining internal equilibrium, including autophagy, proteostasis, and genomic integrity. These improvements, in turn, contribute to mitochondrial resilience and intercellular communication, initiating a self-sustaining loop essential for tissue homeostasis.

By improving the bioavailability and amplifying the biological impact of DNA-S within a natural biomimetic environment, this strategy offers a comprehensive, multi-level approach to promote skin vitality, resilience, and long-term longevity.

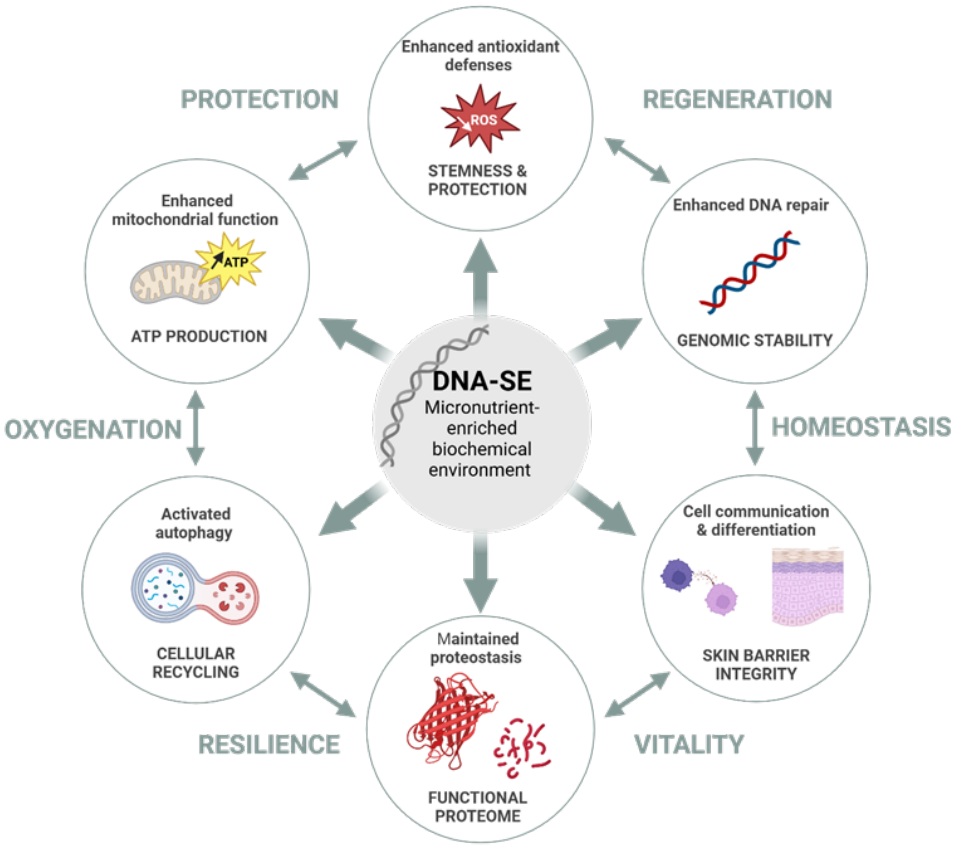

Figure 1. **DNA-SE targets multiple hallmarks of skin aging through interconnected biological pathways.**

DNA-SE enhances mitochondrial function and ATP production, activates autophagy and cellular recycling, supports proteostasis, and strengthens antioxidant defenses. These processes collectively promote cellular resilience and protection. In parallel, DNA-SE reinforces DNA repair and genomic stability, preserves stem cell function, and boosts cell communication and differentiation, contributing to improved skin barrier integrity, tissue homeostasis, and overall vitality. The interdependence of these pathways initiates a virtuous, self-sustaining cycle that maintains cellular balance and functionality. Altogether, DNA-SE offers a comprehensive, multi-targeted strategy to promote skin health, vitality, and longevity. Figure created with Biorender.com

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CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

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