

## Commentary

### Dermal-Epidermal Junction Proteins: A Useful Target for Addressing Age-Related Changes in Facial Skin

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Skin aging is a natural physiological process that occurs due to intrinsic and extrinsic factors. Intrinsic aging of the skin is a well-balanced genetic process affected due to degeneration of skin tissues, hormonal changes, and a natural inability to repair skin damage [1]. Extrinsic factors involve modifiable lifestyle and environmental factors such as smoking, pollution, poor nutrition, and prolonged sun exposure. These factors result in dry and thin skin, flattening skin, wrinkles, rough texture, and facial sagging [1]. The human desire to look young daily makes addressing these skin issues necessary. Conventional skin-care products based on retinol, hyaluronic acid, and alpha and beta hydroxy acids have been used for facial wrinkles and sagging. Increased pollution, exposure to toxins, and ultraviolet irradiations cause skin damage [2]. Previously, skin formulations were based on ascorbic acid, tocopherol, niacinamide, retinyl palmitate, anti-aging peptides, and proteins as topical solutions that reduce Reactive Oxygen Species (ROS) [3]. Currently, green cosmetic awareness has led to plant-based skin care products that include anti-aging properties and pharmacological actions such as anti-allergy, pro-collagen, anti-inflammatory and anti-carcinogenic, UV-protective [4]. The Dermal-Epidermal Junction (DEJ) is a distinct interconnective network complex between the dermis and epidermis that has multiple roles in skin homeostasis and function [5]. Hence, the commentary highlights the significance of dermal-epidermal junction proteins, specifically collagen IV, a target of a newly developed complex DL-linefade. It enhances the performance of niacinamide-based skin formulations by acting synergistically and inducing collagen IV biosynthesis.

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### Dermal-Epidermal Junction and Its Proteins

There is growing evidence that the Dermal-Epidermal Junction (DEJ) and its proteins are a target of oxidative stress autophagy, matrix metalloproteinases, and senescence [6]. A dermal-epidermal junction is an important interface of the skin with four distinct zones, Basement Membrane (BM), Hemidesmosomes (HD), Lamina Lucida (LL), and Lamina Densa (LD) [7]. These zones are mainly composed of collagen IV, plectin, laminin (proteins of BM), and nidogen in the upper regions, collagen IV, VI, anchoring fibrils, and heparan sulfate proteoglycan (proteins of LD) [8]. The interconnecting complex meshwork of DEJ proteins and the finger-like rete ridges aid in maintaining the skin's structural integrity and mechanical stability. The DEJ starts flattening out, its proteins start thinning, the surface area gets reduced, and there is a loss of rete ridges [7]. DEJ changes such as membrane thickness loss, rete ridges flattening, disorganization of lamina lucida, lamina densa, and anchoring filaments contribute significantly towards increased skin fragility in the aged population [8].

Collagen IV is a known significant anchoring protein found in the lamina densa region of the DEJ that provides a framework to the interconnecting network of dermis-epidermis. It plays a vital role in wound healing and enhances cell adhesion and proliferation [1]. Previous studies have reported significantly reduced collagen IV levels in the non-photodamaged elderly than in younger individuals [7].

### Niacinamide: A Boon for Anti-Aging Skin

Facial skin issues have been the major target of many dermatologically tested niacinamide-based skin products [9]. The rationale is these products are beneficial for reducing facial wrinkles and sagging [9]. Although these products help treat skin issues, niacinamide usually targets the collagen I and III proteins of the inner dermal layer of the skin that causes skin aging [9]. It is known that when the skin ages, the collagen proteins deteriorate further; hence, we notice changes in the structure in the elderly with wrinkles, face thinning, dry skin, and sagging [9]. Niacinamide-based skin formulations have been popular due to their versatility, anti-aging properties, and lesser or minimal side effects.

### DL-Linefade: A Novel Complex for Collagen IV Biosynthesis

Collagen IV in the DEJ gets depleted as the non-photodamaged skin aging occurs chronologically [8]. The experiments conducted by Majewski, et al. showed that Linefade could significantly induce collagen IV in cell culture models of Human Dermal Fibroblasts (HDFs) and epidermal skin explants [8].

Peroxisomal proliferator-activated receptor- $\alpha$  (PPAR- $\alpha$ ) is a vital regulator of intrinsic skin aging processes that can bind to multiple ligand complexes. It is a nuclear hormone receptor involved in ligand-activated transcription and regulates various metabolic activities of skin cell types [1]. A plant-derived peroxisomal proliferator-activated receptor- $\alpha$  (PPAR- $\alpha$ ) activator complex, DL-Linefade, was

developed to potentially induce collagen IV synthesis and increase its level in DEJ regardless of age [1]. The synergistic effects of DL-linefade and niacinamide were studied for cooperative binding and gene expression that targets collagen IV synthesis. It was extensively studied by Majewski, et al. in an open observational and single-blinded randomized split-face image analysis study to examine its combined effects on aging skin [8]. The location of collagen IV in the DEJ is an added advantage for DL-Linefade to stimulate its synthesis. This benefits the skin more as opposed to niacinamide targeting the inner layers of the dermis (collagen I and III) [9].

The study by Majewski, et al. compared the effects of two types of formulations in an image analysis study. Product A cream was composed of a combination of (2% Linefade + 3% Niacinamide) and product B cream (3% Niacinamide) [8]. Both formulations were tested for Crow's feet wrinkles, skin roughness, and jaw contour sagging. The intra-group and inter-group analyses on Day 15, Day 30, and Day 45, compared to Day 0, demonstrated significant changes in both group results [8]. There was a significant reduction in Crow's feet roughness, jaw contour sagging, and wrinkles in the tested skin area when the combined product A was applied than product B with only Niacinamide [8]. Although the study's sample size was limited to 20 individuals, this research demonstrated that a plant-derived PPAR- $\alpha$  agonist complex Linefade can improve the niacinamide performance when added to a skin-care product [8].

Hence, it is important to target various DEJ proteins, such as collagen IV, characteristic of skin aging and provide an advantage to manage changes related to skin aging. A novel plant-based collagen regulator as Linefade showed increased potency for multiple ligand binding and induced collagen IV biosynthesis *in vitro* and *ex vivo*. Linefade's mechanism of action included several modulations of transcription factor precursor genes for proteins pertinent to DEJ, epidermal differentiation, and keratinocyte proline-rich protein. Further, this complex could downregulate the collagen-degrading proteins, slowing down the process, which may enhance and maintain collagen IV biosynthesis [1].

## Conclusion

Addressing age-related changes in facial skin requires an interdisciplinary approach targeting DEJ proteins, including collagen IV. Skin aging occurs as part of natural and external forces such as sun exposure and lifestyle decisions; over time, this leads to skin damage such as wrinkles and sagging. Dermacare products with ingredients

like retinol, hyaluronic acid, and antioxidants were once commonly prescribed to address such concerns; however, due to consumer demand for natural and healthy formulations, niacinamide-based formulations have long been utilized for their anti-aging effects, specifically targeting collagen I and III in the dermal layer. Our finding with DL-Linefade, which works synergistically with niacinamide to specifically induce collagen IV biosynthesis at DEJs, can bring a fresh dimension to this domain. This plant-derived PPAR- $\alpha$  peroxisomal activator complex has shown impressive results in improving the efficacy of products based on niacinamide by stimulating collagen IV synthesis. Combining DL-Linefade and niacinamide has shown promising improvements to skin texture, wrinkles, and sagging, providing an effective anti-aging skincare formulation option. More research needs to be conducted to explore its full potential as an anti-aging treatment strategy along with expanded research into other DEJ targets.

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