A Pilot Study on the Effect of Interleukin-1 alpha on Collagen Deposition in Aging Skin

Peter Schoch and Igor Pomytkin, United Cosmeceuticals GmbH, 8002 Zurich, Switzerland

Introduction and Hypothesis

Interleukin-1 alpha (IL-1a) is a cytokine, which has in its mature form 159 amino acids and a molecular weight of about 18 kD. It is highly and constitutively expressed by keratinocytes in the epidermis. As a matter of fact, the epidermis, in particular the stratum corneum, is the tissue which contains by far the highest content of IL-1a in the human body. Interleukin-1 alpha is therefore often referred to as *epidermal cytokine*.

The expression of IL-1a by keratinocytes is subject to positive feedback control, i.e. IL-1a stimulates keratinocytes to express IL-1a.

Various impacts on skin, e.g. physical (injury, UV light), chemical and biological (infections) have been shown to release IL-1a from its intracellular depot.

The target cells of epidermal interleukin-1 alpha are dermal fibroblasts. IL-1a does not only stimulate their proliferation but also activates, in a concentration-dependent manner, the production of procollagen and tropoelastin, hyaluronic acid as well as the expression of several growth and differentiation factors for epidermal cells. Only at low concentrations does IL-1a induce the expression of the tissue inhibitor of metalloproteinase (TIMP, inhibitor of collagenase), thus shifting the balance between the production and degradation of collagen towards production. Therefore, only low doses of IL-1a are beneficial for collagen replenishment in skin.

Based on these findings we proposed a model of IL-1a present in the outer skin (in particular in corneocytes) to act as *sensor* of 'injury', which upon release provides the *signal* for skin renewal after reaching the fibroblasts in the dermis. This model depends on the IL-1a cascade which is kicked off on the surface and penetrates deep into skin by a self-sustaining trigger-release mechanism.

Aim

To test the above described model based on epithelial/mesenchymal interactions initiated by IL-1a on the surface of skin and triggering eventually collagen replenishment in the dermis we performed a pilot study by topically administering IL-1a and measuring the collagen content in the dermis by 2-photon fluorescence microscopy.

Methods

A placebo-controlled pilot study on the collagen and elastin content in the dermis was conducted in volunteers of 63 and 64 years of age by administering an aqueous gel with and without IL-1a (EVENSWISS with Dermatopoietin®) twice daily upon the forearm and measuring the skin structure by 2-photon fluorescence microscopy. In addition to IL-1a the verum gel also contained Hexadeltine, a Leu-enkephalin analogue, to control the release of endogenous IL-1a by keratinocytes. Elastin was monitored by its green autofluorescence, collagen by the red 'second harmonic generation'. The study was performed by Neurotar, Helsinki.

Results

Compared to baseline and placebo the topical administration of a gel containing 150 ng/ml IL-1a (and 200 µg/ml Hexadeltine) led to a significant increase of collagen and elastin. This increase was statistically significant after one week and reached a maximum after 4 weeks.

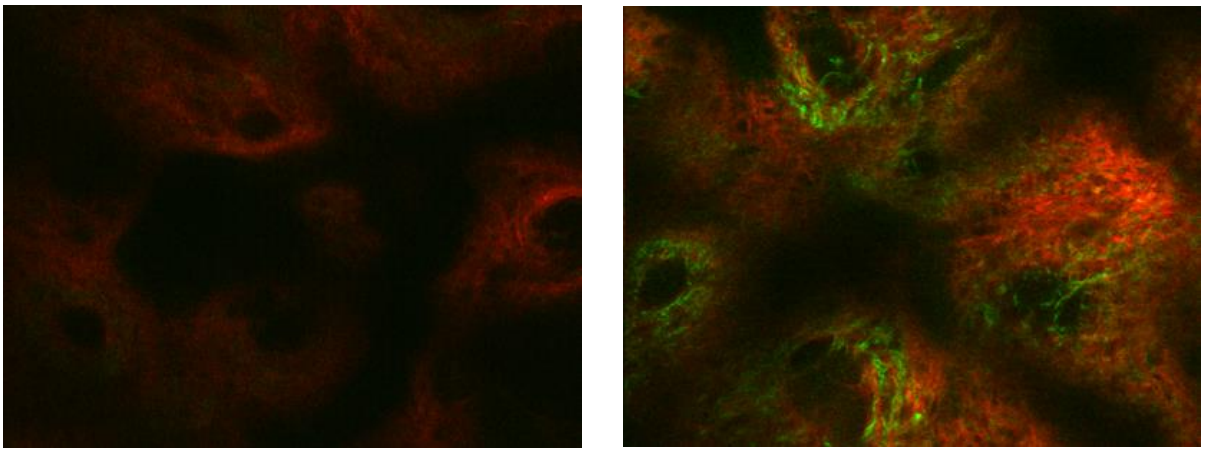

Figure 1. Two-photon-fluorescence microscopic pictures of the forearm skin of a human volunteer 63 years of age at a depth of 80 µm. Green autofluorescence is from elastin, red colour is the second harmonic generation reflecting collagen. Left: Baseline (Day 0). Right: After 4 weeks of twice-daily topical administration of a gel containing 150 ng/ml IL-1a.

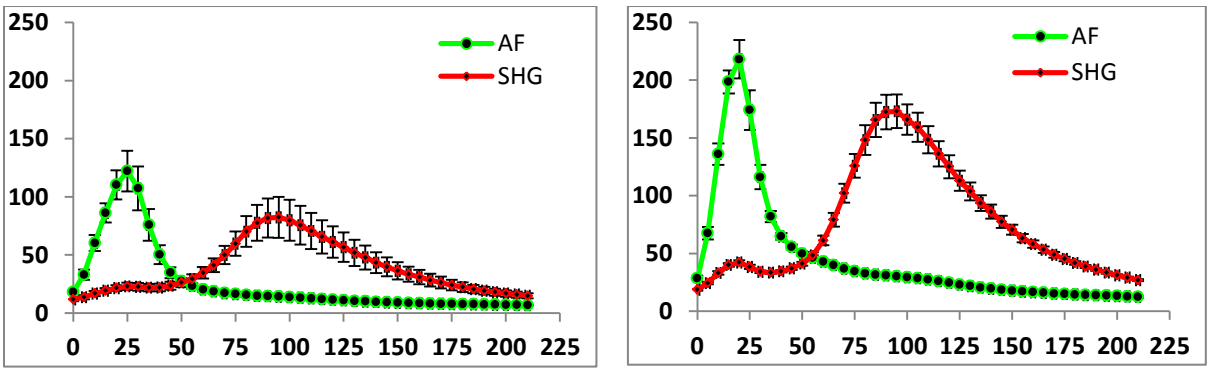

Figure 2. Quantitative evaluation of 2-photon microscopic pictures. Ordinate: Signal strength, arbitrary units. Abscissa: Skin depth in µm. Border between epidermis and dermis at approximately 50 µm. Green curve: Autofluorescence (AF) of keratin in the epidermis and of elastin in the dermis. Red curve: Second Harmonic Generation (SHG) reflecting collagen in the dermis. Left: Baseline. Right: After 2 weeks of twice-daily topical administration of a gel containing 30 ng/ml IL-1a. The contents of collagen and elastin approximately doubled after two weeks compared to placebo or baseline.

Conclusion

Topical administration of IL-1a, which due to its molecular size cannot penetrate skin, leads to a remote effect in the dermis as demonstrated by a significant replenishment of collagen and elastin. This finding supports the hypothesis that IL-1a acts as *sensor* of wear and tear of skin and as *signal* in the dermis for the structural and functional homeostasis of skin. In view of the decreased collagen production in chronologically and environmentally aged skin, IL-1a may have a role as ‘cosmeceutical’ for the treatment of this condition.

References

- Barland C O et al., J Invest Dermatol 2004, 122 : 330. Imiquimod-induced IL-1 alpha stimulation improves barrier homeostasis in aged murine epidermis
- Boxman I et. al., J Invest Dermatol. 1993, 101 : 316. Modulation of IL-6 production and IL-1 activity by keratinocyte-fibroblast interaction
- Dae Hun Suh et al., J Clin Dermatol 2001, 117 : 1225. Effects of 12-O-tetradecanoyl-phorbol and sodium lauryl sulfate on the production and expression of cytokines and proto-oncogenes in photoaged and intrinsically aged human keratinocytes
- Duncan M R and Berman B, J Invest Dermatol 1989, 92 : 699. Differential regulation of collagen, glycosaminoglycan, fibronectin, and collagenase activity production in cultures human adult dermal fibroblasts by IL-1 alpha/beta and TNF alpha/beta
- Gahring L C et al., J Clin Invest 1985, 76 : 1585. Presence of epidermal-derived thymocyte activating factor/IL-1 in normal human stratum corneum
- Goldring M B and Krane S M, J Biol Chem 1987, 262 : 16742. Modulation by recombinant IL-1 of synthesis of types I and III collagens and associated procollagen mRNA levels in cultured human cells
- Hauser C et al., J Immunol 1986, 136 : 3317. IL-1 is present in normal human epidermis
- Luger T A and Schwarz T, J Invest Dermatol 1990, 95: 100S. Evidence for an epidermal cytokine network
- Maas-Szabowski N et al., J Invest Dermatol 2000, 114 : 1075. Keratinocyte growth regulation in defined organotypic cultures through IL-1-induced keratinocyte growth factor expression in resting fibroblasts
- Postlethwaite A et al., J Cell Biol 1988, 106 : 311. Modulation of fibroblast functions by IL-1: Increased steady-state accumulation of type I procollagen mRNAs and stimulation of other functions but not chemotaxis by human recombinant IL-1 alpha und IL-1 beta
- Varani J, et a. Am J Pathol 2006, 168 : 1861. Decreased collagen production in aged skin
- Veli-Matti K et al., Biochim Biophys Acta 1987, 929 : 142. IL-1 increases collagen production and mRNA levels in cultures skin fibroblasts
- Werner S and Smola H, Trends in Cell Biol 2001, 11 : 143. Paracrine regulation of keratinocyte proliferation and differentiation
- Wood L C, et al., J Clin Invest 1992, 90 : 482. Cutaneous barrier perturbation stimulates cytokine production in the epidermis of mice
- Ye J et al., Exp Dermatol 2002, 11 : 209. Alterations in cytokine regulation in aged epidermis. Implications for permeability barrier homeostasis and inflammation