I. Pomytkin

Interleukin-1 Alpha, an Epidermal Cytokine Critical for Skin Renewal

Introduction

Interleukin-1 alpha (IL-1 alpha) is an epidermal cytokine. It is constitutively produced by human keratinocytes in substantial amounts and plays an important role in normal skin homeostasis. Before being so named, IL-1 alpha was discovered in 80s as epidermal cell-derived thymocyte-activating factor (ETAF) (1-4). Other cells synthesize and release IL-1 alpha under stimulation. For last three decades both constitutive and inducible IL-1 alpha has been extensively studied by investigators working in such unrelated fields as immunology, hematology, physiology, and dermatology research. Frequently, IL-1 alpha was characterized by names descriptive of their biological properties such as thymocyte-activating factor, lymphocyte activating factor, hematopoietin-1, and etc. The purpose of this minireview is to focus on the properties of IL-1 alpha as the »dermatopoietin«, or the factor that orchestrates entire process of skin renewal through regulation of production secondary regulators such as growth factors, prostaglandins, enzymes and their inhibitors, components of dermis and others molecules involved in epidermal morphogenesis and dermis remodeling.

Interleukin-1 Alpha Family

Interleukin-1 family consists of several polypeptides (5-7). Among them, only IL-1 alpha is produced by keratinocytes in a biologically active form on a constitutive basis (4, 8, 9). It is expressed as 36 kDa pro-protein, processed to mature 17 kDa form by membrane-associated calcium-dependent cysteine protease calpain, and subsequently released to extracellular space (10, 11). Thus, IL-1 biological activity in keratinocytes is only IL-1 alpha activity.

Interleukin-1 Alpha is Constitutively Produced by Human Epidermis

IL-1 alpha was found in substantial amounts in normal human epidermis, about 50:50 in living epidermal cells and stratum corneum (12-14). On a calculation basis, 1 gram of stratum corneum contains about 6000 ng of WHO standard of IL-1 alpha, since about $6x10^5$ IU activity per gram of stratum corneum was found in the specific LAF test (12). For the reference, even 1 ng/kg IL-1 alpha administered intravenously induced fever as the common adverse effect for all patients by results of clinical studies in 90s (15). So, skin-derived IL-1 alpha represents isolated from other body pool, otherwise, as early as 1 ng/kg of skin-derived IL-1 alpha would produce the fever as adverse effect.

Abstract

Interleukin-1 alpha (IL-1 alpha) is an epidermal cytokine that is constitutively produced by human keratinocytes in substantial amounts and plays an important role in normal skin homeostasis. Comprehensive bibliography highlights the role of Interleukin-1 alpha as the master regulator of skin architecture and functions. At picomolar concentrations IL-1 alpha stimulates dermal fibroblasts to produce a cascade of growth factors (KGF, GM-CSF, and HGF) required for keratinocyte growth. IL-1 alpha stimulates collagen turnover in dermis by tight regulation of both collagen synthesis and degradation pathways. IL-1 alpha stimulates dermal fibroblasts to produce glycosaminoglycans, particularly hyaluronic acid. IL-1 alpha plays a role in keeping skin barrier function in norm. IL-1 alpha production and action in skin may be affected by extrinsic or intrinsic factors, e.g. chronologic aging or cortisol action. It provides a basis for the use of recombinant human interleukin-1 alpha as an active ingredient in dermatologic and cosmetic applications with focus on anti-age and anti-cellulite products.

The rate of IL-1 alpha production in skin depends on intrinsic and extrinsic factors. Chronological aging decreases IL-1 alpha production in skin (16-18). Cortisol suppresses constitutive expression of IL-1 alpha in human keratinocytes (19). Recombinant human IL-1 alpha enhances expression of new IL-1 alpha molecules in human keratinocytes in autocrine manner (19). Ultraviolet radiation augments IL-1 alpha gene expression in keratinocytes (20). Glycolic acid, a chemical peeling agent, up-regulates production of IL-1 alpha in skin (21).
Thus, IL-1 alpha is cytokine that is produced almost exclusively in skin epidermis on a whole body production basis and the rate of such production could be modulated by intrinsic or extrinsic factors.

Dermal Fibroblasts are Primary Target of Interleukin-1 Alpha

Dermal fibroblasts are paracrine target of keratinocyte-derived IL-1 alpha. IL-1 alpha induces proliferation of dermal fibroblasts (22). At picomolar concentrations IL-1 alpha stimulates dermal fibroblasts to produce a cascade of autocrine and paracrine regulators, extracellular matrix components, enzymes, and other molecules required for epidermis and dermis regeneration.

Interleukin-1 Alpha Plays a Role in Normal Epidermal Morphogenesis

It is well-documented that IL-1 alpha is a primary inductor of epidermis renewal (23-27). IL-1 alpha does not stimulate keratinocyte growth directly, but induces it indirectly through a double paracrine regulatory mechanism **(Fig. 1)**. Keratinocyte-derived IL-1 alpha stimulates dermal fibroblasts to express and release a set of growth factors critical for basal keratinocyte proliferation and differentiation. These growth factors, in turn, stimulate keratinocyte proliferation and differentiation in a paracrine manner. Such growth factors are granulocyte-macrophage colony stimulating factor (GM-CSF), hepatocyte growth factor (HGF), and keratinocyte growth factor (KGF).

The significance of the IL-1 action for epidermal regeneration has been confirmed by: (i) inhibition of KGF release and keratinocyte proliferation by interleukin-1 receptor antagonist and IL-1-neutralizing antibodies; and (ii) restoration of impaired epidermal morphogenesis by stimulation with IL-1 [25].

Interleukin-1 Alpha Stimulates Collagen Turnover in Dermis

IL-1 alpha stimulates dermal fibroblasts to produce precursors of collagen synthesis, procollagen type I and III, and PGE2, an inhibitor of procollagen conversion to collagen (22, 28). In parallel, IL-1 alpha stimulates production of collagenase and the collagenase inhibitor TIMP (tissue inhibitor of metalloproteinase) (22, 29). Taken together, it indicates that IL-1 alpha orchestrates collagen turnover in dermis through complex regulation of both collagen synthesis and degradation pathways. Integrally, IL-1 alpha-stimulated collagen production is described by a bell-shaped dose-dependent curve with maximal response at about one picomole of IL-1 alpha (22). At this concentration, IL-1 alpha stimulates 1.7-fold the collagen production, about 2-fold the synthesis and accumulation of type I procollagen chains, 8-fold the collagenase production and 7-fold the TIMP production, while remains unaltered the relative rate of intracellular collagen degradation.
Interestingly, the effect of IL-1 alpha on collagen production/degradation is distinct of that is produced IL-1 beta, a monocyte-derived IL-1 isoform. Although IL-1 beta dramatically stimulates collagenase production by dermal fibroblasts, it has no significant effect on TIMP production. It suggests that IL-1 beta is involved predominantly in degradation rather than collagen synthesis (22).
Thus, IL-1 alpha orchestrates turnover of collagen in dermis by tight regulation of both collagen synthesis and degradation pathways **(Fig. 2)**.

Interleukin-1 Alpha Effects on Other Extracellular Matrix Components of Dermis

IL-1 alpha does not stimulate noncollagenous protein synthesis, e.g. fibronectin and beta-actin (22), and even suppresses fibronectin production when taken at high concentrations (29). IL-1 alpha stimulates dermal fibroblasts to produce glycosaminoglycans, particularly hyaluronic acid (29, 30).

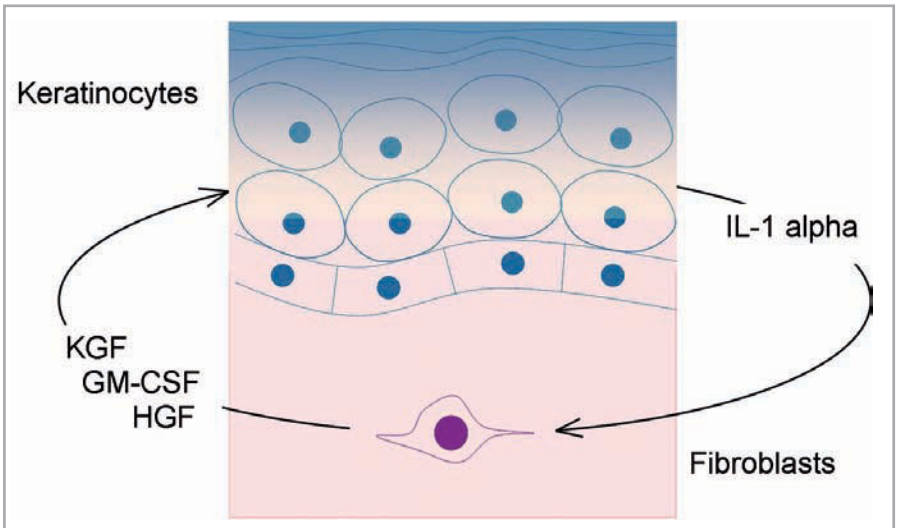

Fig. 1 Scheme of a double paracrine regulatory mechanism of epidermis renewal. Keratinocyte-derived IL-1 alpha stimulates dermal fibroblasts to express and release a set of growth factors, e.g. KGF, GM-CSF, and HGF. These factors, in turn, stimulate keratinocyte proliferation and differentiation in a paracrine manner

Interleukin-1 Alpha Effects on Melanogenesis

IL-1 alpha inhibits melanocyte proliferation and melanogenesis (31). The IL-1 alpha effect on melanocyte proliferation is reversible and cytostatic rather than cytotoxic. At picomolar concentrations, IL-1 alpha inhibits activity of tyrosinase, the key enzyme of melanin production **(Fig. 3)**.
IL-1 alpha may activate melanogenesis through stimulation of melanogenesis activators and their receptors on melanocytes. IL-1 alpha induces expression of proopiomelanocortin (POMC), a precursor for adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormones (MSH), beta-lipotropic hormone (beta LPH), and beta endorphin, potent activators of melanocyte proliferation and melanogenesis (32). IL-1 alpha induces about 12-fold increase in secretion of endothelin-1 (ET-1), the potent activator of melanogenesis, from human keratinocytes (33). IL-1 alpha up-regulate expression of the MC-1 gene and of functional cell surface MSH receptors in normal melanocytes (34).

Interleukin-1 Alpha Plays a Role in Regulation of Skin Barrier Function

Growing evidence suggests that IL-1 alpha plays a role in keeping skin barrier function in norm **(Fig. 4)**. Age-related abnormalities of IL-1 alpha production and action may contribute to the decline of permeability barrier function. Acute disruption of the barrier by either acetone or tape stripping increases the epidermal levels of IL-1 alpha mRNA (35). Aged epidermis modulates both IL-1 alpha production and IL-1 receptor expression abnormally following barrier perturbation (36). Intracutaneous administration of IL-1 alpha accelerates epidermal permeability barrier recovery in both young and aged skin, with more significant improvement in aged skin. This effect is achieved through an enhancement of lipid synthesis and normalization of lammelar bilayer structure in epidermis (37).

Conclusions and Perspectives

Comprehensive bibliography highlights the role of Interleukin-1 alpha as the master regulator of skin architecture and functions. Keratinocyte-derived IL-1 alpha represents isolated from other body pool of biologically active IL-1 alpha. It orchestrates epidermal morphogenesis and dermis remodeling, and plays a role in keeping in norm skin barrier function. Interleukin-1 alpha is the epidermal cytokine that is produced constitutively in epidermis in biologically active form. IL-1 alpha production and action in skin may be affected by extrinsic or intrinsic factors, e.g. chronologic aging or cortisol action. Excessive cortisol activity is frequently accompanied with metabolic syndrome and obesity, widely distributed in western countries. Cortisol is produced by fat cells in response to estrogens and may contribute to skin abnormalities caused by excessive accumulation of regional fat in women, e.g. under cellulite. It provides a basis for the use of recombinant human interleukin-1 alpha as an active ingredient in dermatologic and cosmetic applications with focus on anti-age and anti-cellulite products

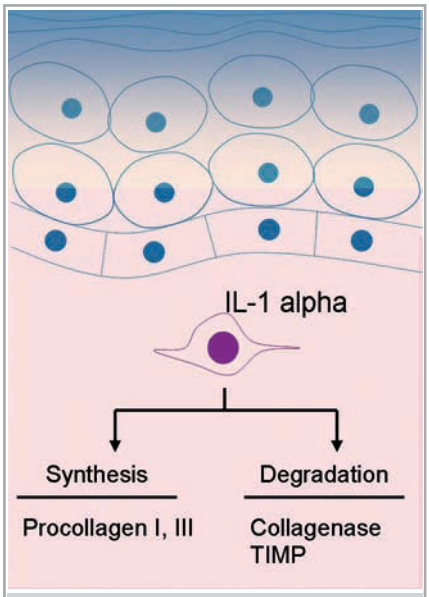

Fig. 2 IL-1 alpha orchestrates collagen turnover in dermis by tight regulation of both collagen synthesis and degradation pathways. Keratinocyte-derived IL-1 alpha stimulates dermal fibroblasts to express and release type I and III procollagen, precursors of matrix collagen. Besides that, IL-1 alpha stimulates production of collagenase and its inhibitor TIMP for tight regulation of collagen degradation

References

(1) *Luger TA, Stadler BM, Katz SI, Oppenheim JJ.* Epidermal cell (keratinocyte)-derived thymocyte-activating factor (ETAF). J. Immunol. 1981, 127(4): 1493-8

(2) *Sauder DN, Carter CS, Katz SI, Oppenheim JJ.* Epidermal cell production of thymocyte activating factor (ETAF). J. Invest Dermatol. 1982, 79(1):34-9

(3) *Kupper TS, Ballard DW, Chua AO, McGuire JS, Flood PM, Horowitz MC, Langdon R, Lightfoot L, Gubler U.* Human keratinocytes contain mRNA indistinguishable from monocyte in-

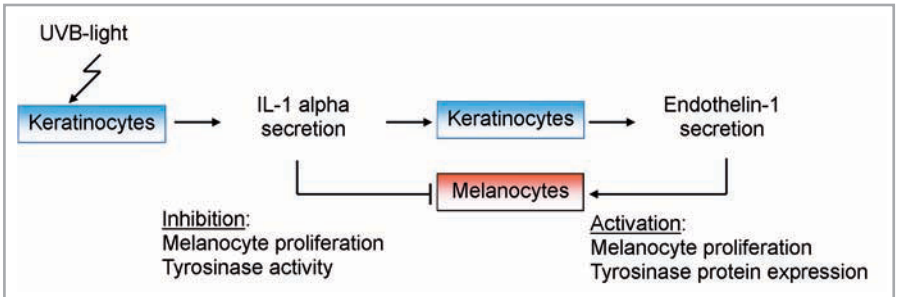

Fig. 3 IL-1 alpha is involved in the regulation of melanogenesis. Keratinocytes secrete IL-1 alpha upon exposure to UVB. IL-1 alpha directly inhibits melanogenesis through inhibition of melanocyte proliferation and tyrosinase activity. UVB-induced IL-1 alpha stimulates expression and secretion of Endothelin-1, which, in turn, activates melanocyte proliferation and tyrosinase protein expression

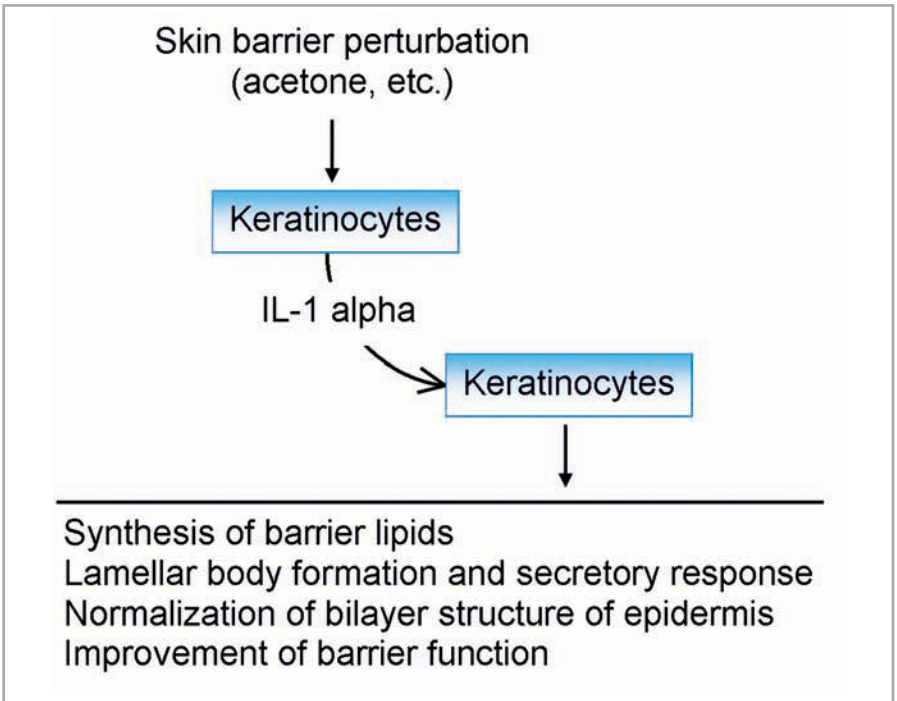

Abb. 4 IL-1 alpha ist involiert in der Wiederherstellung der Hautbarrierefunktion. Akute Störungen der Barriere führen zur Ausschüttung von IL-1 alpha. Dieses stimuliert im Gegenzug die Lipidsynthese und Normalisierung der lamellaren Doppelschichtstruktur der Epidermis. Insgesamt resultieren diese Prozesse in der Verbesserung der Hautbarrierefunktion

terleukin 1 alpha and beta mRNA. Keratinocyte epidermal cell-derived thymocyte-activating factor is identical to interleukin 1. J. Exp. Med. 1986, 164(6):2095-100

(4) *Kupper TS, Ballard D, Chua AO, McGuire J, Flood P, Horowitz M, Langdon R,* and *Gubler U.* Human keratinocytes contain mRNA indistinguishable from monocyte interleukin I alpha and beta mRNA. J. Exp. Med. 1986, 69: 2095-2100

(5) *Sims JE, Nicklin MJ, Bazan JF, Barton JL, Busfield SJ, Ford JE, Kastelein RA, Kumar S, Lin H, Mulero JJ, Pan J, Pan Y, Smith DE, Young PR.* A new nomenclature for IL-1-family genes. Trends Immunol. 2001, 22(10):536-7

(6) *Dinarello CA.* The interleukin-1 family: 10 years of discovery. FASEB J. 1994, 8:1314-1325

(7) *Lomedico PT, Gubler U, Hellmann CP, Dukovich M, Giri JG, Pan YC, Collier K, Semionow R, Chua AO, Mizel SB.* Cloning and expression of murine interleukin-1 cDNA in Escherichia coli. Nature 1984, 312(5993):458-62

(8) *Cooper K, Hammerberg C, Baadsgaard O, Elder J, Chan L, Sauder D, Voorhees J,* and *Fisher G.* IL-I activity is reduced in psoriatic skin: decreased IL-I alpha and increased non-functional IL-I beta. J. Immunol. 144:4593-4598

(9) *Kupper TS.* Hematopoietic, lymphopoietic, and proinflammatory cytokines produced by keratinocytes. Ann. NYAcad. Sci. 1988, 548:262-270

(10) *Kobayashi Y, Yamamoto K, Saido T, Kawasaki H, Oppenheim JJ, Matsushima K.* Identification of calcium-activated neutral protease as a processing enzyme of human interleukin 1 alpha. PNAS, 1990, 87, 5548

(11) *Mizutani H, Black R, Kupper TS.* Human keratinocytes produce but do not process pro-interleukin-1 (IL-1) beta. Different strategies of IL-1 production and processing in monocytes and keratinocytes. J. Clin. Invest. 1991, 87(3): 1066-71

(12) *Gahring LC, Buckley A, Daynes RA.* Presence of epidermal-derived thymocyte activating factor/interleukin 1 in normal human stratum corneum. J. Clin. Invest. 1985 76(4): 1585-91

(13) *Hauser C, Saurat JH, Schmitt A, Jaunin F, Dayer JM.* Interleukin 1 is present in normal human epidermis. J. Immunol. 1986, 136(9): 3317-23

(14) *Schmitt A, Hauser C, Jaunin F, Dayer JM, Saurat JH.* Normal epidermis contains high amounts of natural tissue IL 1 biochemical analysis by HPLC identifies a MW approximately 17 Kd form with a pH 5.7 and a MW approximately 30 Kd form. Lymphokine Res. 1986, 5(2):105-18

(15) *Veltri S, Smith II JW.* Interleukin 1 trials in cancer patients: a review of the toxicity, antitumor, and hematopoietic effects. Stem Cells 1996, 14:164-176

(16) *Sauder DN, Stanulis-Praeger BM, Gilchrest BA.* Autocrine growth stimulation of human keratinocytes by epidermal cell-derived thymocyte-activating factor: implications for skin aging. Arch. Dermatol. Res. 1988, 80(2): 71-6

(17) *Sauder DN.* Effect of age on epidermal immune function. Dermatol. Clin. 1986, 4(3): 447-54

(18) *Barland CO, Zettersten E, Brown BS, Ye J, Elias PM, Ghadially R.* Imiquimod-induced interleukin-1 alpha stimulation improves barrier homeostasis in aged murine epidermis. J. Invest. Dermatol. 2004, 122(2):330-6

(19) *Lee SW, Morhenn VB, Ilnicka M, Eugui EM, Allison AC.* Autocrine stimulation of interleukin-1 alpha and transforming growth factor alpha production in human keratinocytes and its antagonism by glucocorticoids. J. Invest. Dermatol. 1991, 97(1):106-10

(20) *Kupper TS, Chua AO, Flood P, McGuire J, Gubler U.* Interleukin 1 gene expression in cultured human keratinocytes is augmented by ultraviolet irradiation. J. Clin. Invest. 1987, 80(2):430-6

(21) *Jeong SK, Ko JY, Seo JT, Ahn SK, Lee CW, Lee SH.* Stimulation of epidermal calcium gradient loss and increase in TNF-alpha and IL-1alpha expressions by glycolic acid in murine epidermis. Exp. Dermatol. 2005, 14(8):571-9

(22) *Postlethwaite AE, Raghow R, Stricklin GP, Poppleton H, Seyer JM, Kang AH.* Modulation of fibroblast functions by interleukin 1: increased steady-state accumulation of type I procollagen messenger RNAs and stimulation of other functions but not chemotaxis by human recombinant interleukin 1 alpha and beta. J. Cell. Biol. 1988, 106(2):311-8

(23) *Maas-Szabowski N, Shimotoyodome A, Fusenig NE.* Keratinocyte growth regulation in fibroblast cocultures via a double paracrine mechanism. J. Cell. Sci. 1999, 112 (Pt 12): 1843-53

(24) *Szabowski A, Maas-Szabowski N, Andrecht S, Kolbus A, Schorpp-Kistner M, Fusenig NE,* Angel P. c-Jun and JunB antagonistically control cytokine-regulated mesenchymal-epidermal interaction in skin. Cell 2000, 103(5):745-55

(25) *Maas-Szabowski N, Stark HJ, Fusenig NE.* Keratinocyte growth regulation in defined

organotypic cultures through IL-1-induced keratinocyte growth factor expression in resting fibroblasts. J. Invest. Dermatol. 2000, 114(6): 1075-84

(26) *Werner S.* and *Smola H.* Paracrine regulation of keratinocyte proliferation and differentiation. Trends Cell. Biol. 2001, 11(4):143-146

(27) *Werner, S.* Keratinocyte growth factor: A unique player in epithelial repair processes. 1998, Cytokine Growth Factor Rev. 9, 153-165

(28) *Mauviel A, Heino J, Kähäri VM, Hartmann DJ, Loyau G, Pujol JP, Vuorio E.* Comparative effects of interleukin-1 and tumor necrosis factor-alpha on collagen production and corresponding procollagen mRNA levels in human dermal fibroblasts. J. Invest. Dermatol. 1991, 96(2):243-9

(29) *Duncan MR, Berman B.* Differential regulation of collagen, glycosaminoglycan, fibronectin, and collagenase activity production in cultured human adult dermal fibroblasts by interleukin 1-alpha and beta and tumor necrosis factor-alpha and beta. J. Invest. Dermatol. 1989, 92(5):699-706

(30) *Postlethwaite AE, Smith GN Jr, Lachman LB, Endres RO, Poppleton HM, Hasty KA, Seyer JM, Kang AH.* Stimulation of glycosaminoglycan synthesis in cultured human dermal fibroblasts by interleukin 1. Induction of hyaluronic acid synthesis by natural and recombinant interleukin 1s and synthetic interleukin 1 beta peptide 163-171. J. Clin. Invest. 1989, 83(2):629-36

(31) *Swope VB, Abdel-Malek Z, Kassem LM, Nordlund JJ.* Interleukins 1 alpha and 6 and tumor necrosis factor-alpha are paracrine inhibitors of human melanocyte proliferation and melanogenesis. J. Invest. Dermatol. 1991, 96(2):180-5

(32) *Wintzen M, Yaar M, Burbach JP, Gilchrest BA.* Proopiomelanocortin gene product regulation in keratinocytes. J. Invest. Dermatol. 1996, 106(4):673-8

(33) *Imokawa G, Yada Y, Miyagishi M.* Endothelins secreted from human keratinocytes are intrinsic mitogens for human melanocytes. J. Biol. Chem. 1992, 267(34):24675-80

(34) *Slominski A, Wortsman J.* Neuroendocrinology of the skin. Endocr. Rev. 2000, 21(5):457-87

(35) *Wood LC, Jackson SM, Elias PM, Grunfeld C, Feingold KR*: Cutaneous barrier perturbation stimulates cytokine production in the epidermis of mice. J. Clin. Invest. 90:482-487, 1992

(36) *Ye J, Garg A, Calhoun C, Feingold KR, Elias PM, Ghadially R*: Alterations in cytokine regulation in aged epidermis: Implications for permeability barrier homeostasis and inflammation. I. IL-1 gene family. Exp. Dermatol. 11: 209-216, 2002

(37) *Barland CO, Zettersten E, Brown BS, Ye J, Elias PM, Ghadially R.* Imiquimod-induced interleukin-1 alpha stimulation improves barrier homeostasis in aged murine epidermis. J. Invest. Dermatol. 2004, 122(2):330-6

Author's address:
Dr. Igor Pomytkin
United Cosmeceuticals GmbH
Wagistrasse 13
8952 Schlieren/Zurich,
Switzerland

* *Contact*
Irina Voss
United Cosmeceuticals GmbH
Wagisstrasse 13
8952 Schlieren/Zurich,
Switzerland
Email: i.voss@unicos.ch