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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 6x10^3 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 (IGF, 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. chronic 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).

**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. Integranly, 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, 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).

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**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 lamellar 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. chronic 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.

References

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

**Abb. 4** IL-1 alpha ist involviert 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.

**Skin barrier perturbation (acetone, etc.)**

**Keratinocytes**

IL-1 alpha

**Keratinocytes**

**Synthesis of barrier lipids**

**Lamellar body formation and secretory response**

**Normalization of bilayer structure of epidermis**

**Improvement of barrier function**

**Abb. 4** IL-1 alpha is involved in the restoration of the skin barrier function. Acute barrier disturbances lead to the release of IL-1 alpha. This stimulates in turn the lipid synthesis and normalization of the lamellar bilayer structure of the epidermis. Overall, these processes result in the improvement of the skin barrier function.

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


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