

The Role of Interleukin-1 alpha in the Regulation of the Hair Cycle

In the following the experimental data about the role of IL-1 alpha in the regulation of the hair cycle are summarized.

Background

In normal human epidermis IL-1 alpha is produced constitutively by human keratinocytes in substantial amounts (for a review see [22]). Growing evidence suggests that it plays an essential role in normal skin development. The opinion that IL-1 alpha is simply a “pro-inflammatory” cytokine does not correspond to the current state of knowledge. As pleiotropic factor IL-1 alpha is expressed in many tissues with different, site-specific effects.

In normal human epidermis 50% of IL-1 alpha present is found in stratum corneum and 50% in living cells. Stratum corneum contains about 600 ng/g of IL-1 alpha, since about 6×10^5 IU activity per gram of stratum corneum was found in the specific LAF (lymphocyte-activating factor) test. All IL-1 activity in healthy human skin is IL-1 alpha activity. As reference, the normal blood level of IL-1 alpha is about 2 pg/ml. On a quantitative basis IL-1 alpha is thus predominantly produced in skin which represents an isolated pool from the rest of the body.

IL-1 alpha functions in skin include the induction of epidermal growth through epithelial-mesenchymal interactions, the regulation of skin barrier function (lipid biosynthesis) and the regulation of the synthesis of extracellular matrix components in dermis.

In contrast, the IL-1 beta isoform is the inducible form of IL-1 that is produced by mesenchymal cells upon stimulation. It has 26% identity with IL-1 alpha. Although the general opinion is that IL-1 alpha and beta effects are indistinguishable, there are data that this is not so.

Published data about the role of IL-1 alpha in hair biology is summarized below.

In vitro data

Hair follicle culture

- IL-1 alpha has been shown to inhibit human hair follicle growth, the primary effect being the inhibition of matrix keratinocyte proliferation [1]. In a second article, the same authors conclude that IL-1 alpha has no direct effect on hair fiber growth. The inhibitory effect of IL-1 alpha on hair fiber growth is explained by an inhibition of the proliferation of epithelial matrix keratinocytes: “the depletion of the pool of differentiated follicular keratinocytes capable of elaborating hair fibre” [2].
- IL-1 beta has been shown to inhibit human hair follicle growth; this effect is mediated by cyclic AMP [3].

Follicular papilla cells

- Upon stimulation with IL-1 alpha, follicular papilla cells have been shown to increase the synthesis of a set of factors vital for hair growth, e.g. keratinocyte growth factors (KGF), granulocyte-macrophage stimulating factor (GM-CSF), and vascular endothelial growth factor (VEGF) [4].
- KGF is an activator of follicular keratinocyte proliferation, mediator of hair follicle growth, development and differentiation and an inducer of extensive hair growth at the site of injection in animal models of alopecia [5].
- KGF protected hair follicles from death induced by UV light, cytotoxic agents, and chemotherapy [6].
- VEGF is responsible for maintaining proper vasculature around the hair follicle during the anagen growth phase [7, 8]. Minoxidil up-regulated the VEGF expression [9].
- Upon stimulation with IL-1 alpha, follicular papilla cells have been shown to increase the expression of protease nexin-1 (PN1) [4].
- PN1 is an inhibitor of serine proteases (e.g. thrombin, urokinase, and tPA). PN1 is accumulated in anagen follicular cells and a reliable marker of the anagen phase of hair follicles [10].
- The level of PN1 is down-regulated by androgens [11].
- PN1 was found only in follicles during the anagen but not during the catagen phase [12].
- Stimulation by IL-1 alpha resulted in reduced expression of androgen receptors by follicular papilla cells stimulated by dehydrotestosterone (DHT) [4].
- Androgen receptors are pathologically elevated in androgenetic alopecia [13].
- Upon stimulation with IL-1 alpha, follicular papilla cells have been shown to increase the expression of hepatocyte growth factor (HGF) [14].
- HGF stimulated hair growth and DNA synthesis in hair follicles as well as DNA synthesis in hair bulb-derived keratinocytes [14].

Summary

The effects of IL-1 alpha on hair follicle growth are complex. IL-1 alpha and IL-1 beta directly inhibit the proliferation of matrix keratinocytes. This effect is mediated by cAMP. IL-1 alpha does not inhibit hair fiber growth. But at the same concentration, IL-1 alpha also dramatically stimulates follicular papilla cells to express growth factors (KGF, HGF, GM-CSF, VEGF) required for keratinocyte proliferation, hair follicle development and differentiation which lead to hair growth, hair elongation, and proper vasculature around the hair follicle during the anagen growth phase. IL-1 alpha further stimulates the expression of PN1, the main marker of anagen follicles. PN1 is a serine protease inhibitor with activity against thrombin, plasminogen activators tPA and uPA, trypsin and plasmin. Thrombin is the main target of PN1. Thrombin receptors are present in hair follicles only during the catagen phase. Activated by thrombin they reduce the hair growth-supporting activity of follicle papilla cells (switch to catagen). PN1 co-localizes with thrombin and restricts its activity in follicles [24]. IL-1 alpha suppresses androgen receptor expression by follicular papilla cells, a clear anti-androgenetic alopecia effect. These data suggest that the effects of IL-1 alpha are mediated by follicular papilla cells and that these effects are related to the anagen phase of hair follicles. Taken into consideration that IL-1 alpha is constitutively expressed in substantial amounts by

keratinocytes and that this expression coexists with hair growth, these data strongly suggest a dominant role of IL-1 alpha in the regulation the normal human hair cycle.

As a reference, IL-1 alpha was found to be a key player in the paracrine regulation of epidermis growth:

(i) Keratinocyte-derived IL-1 alpha acts on dermal fibroblasts and up-regulates the expression of growth factors responsible for keratinocyte proliferation and differentiation such as KGF, GM-CSF, and HGF, which in turn, (ii) stimulate epidermal cell growth. IL-1 alpha signaling was found to be vital for epidermis growth, since inhibition of IL-1 action resulted in epidermis degeneration [23]. It must be mentioned that IL-1 alpha does not stimulate keratinocyte proliferation directly.

In vivo animal data

Rats

- Injection of recombinant human IL-1 beta protected newborn rats against 1-beta-D-arabinofuranosylcytosine-induced alopecia [15-17].
- In an animal model of alopecia areata, Dundee experimental balding rats, 0.1% topical anthralin treatment is fully effective in restoring follicular activity. The successful treatment was accompanied with stimulation of interleukin-1 alpha/beta production [18].

Mice

- The immunomodulator AS101 significantly prevented chemotherapy-induced alopecia. The protection was mediated at least in part by IL-1 activity, since an interleukin-1 receptor antagonist (IL-1RA) largely abrogated the effect of AS101 [19].

Transgenic mice

- Transgenic mice overexpressing IL-1 alpha in basal keratinocytes show patchy hair loss [20].

Summary

IL-1 alpha itself or IL-1 alpha inducing agents prevent chemotherapy-induced alopecia and alopecia areata in animal models. It must be emphasized that these agents did not induce hair loss in the above mentioned experiments. The only exceptions are transgenic mice constantly overexpressing IL-1 alpha in skin, a model far from reality.

Human data

Humans

- Phase-I and phase-II clinical studies in cancer patients undergoing chemotherapy demonstrated that AS101 reduced the severity of alopecia. Evidence was presented that the AS101 effects were mediated by IL-1 activity and that there was inverse correlation between the grade of alopecia and the increase in IL-1 alpha. Authors speculated that the anti-alopecia effect of AS101 may be related directly to IL-1 alpha production or, indirectly, to IL-1 alpha-induced PGE2 or KGF [19].

- No elevated levels of IL-1 alpha were found in patients with alopecia areata (AA) as compared to control. So, the link between AA pathogenesis and IL-1 alpha is doubtful [21].
- IL-1 alpha is an epithelial/epidermal cytokine that is constitutively produced by epithelial cells in large amounts (see Background above). The simultaneous occurrence of substantial amounts of IL-1 alpha in normal skin and growing hairs is fact. It does not support the idea of IL-1 alpha being a hair growth inhibiting agent in vivo. On the contrary, the overall evidence of experimental data suggest an important role of IL-1 alpha in the regulation of hair cycles which includes the inhibition of hair loss and the promotion of anagen mechanisms in hair follicles.

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