

# Epidermal Keratinocyte-derived Basophil Promoting Activity

## Role of Interleukin 3 and Soluble CD23

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### Abstract

Human epidermal keratinocytes (EK) secrete factors able to sustain the proliferation of early myeloid cells and, in particular, the generation of basophils. This activity was previously attributed to IL-3, although no definitive *in situ* demonstration of this cytokine was provided. In regard to the possible physiological relevance of these data, we investigated herein the nature of EK-derived factors responsible for basophil promotion. Our data show that EK-derived supernatants (EK-sup) contain IL-3 as well as soluble CD23 (sCD23), both known for their colony stimulating activity. Messenger RNA for IL-3 and CD23 were also detected in EK. Blocking experiments using specific neutralizing monoclonal antibodies (mAb) further indicate that EK-derived basophil promoting activity is mainly due to the presence of IL-3 and sCD23 in EK-sup. Furthermore, by contrast to IL-3, sCD23 secretion by EK is cortisone sensitive and highly enhanced by IL-4, suggesting distinct regulatory mechanisms for their production. (*J. Clin. Invest.* 1992. 90:1242-1247.) Key words: colony-forming units • epithelial cells • bone marrow • FcεRII • basophils

### Introduction

Immunological role of epidermal keratinocytes (EK)<sup>1</sup> remains ill-defined. However, several studies pointed to a remarkable capacity of these cells to secrete a variety of cytokines (1-5). In particular, EK-derived supernatants (EK-sup) could sustain colony generation by early myeloid precursors (4). This activity was suggested to be due to IL-3 because it had biological and biochemical similarities to IL-3 (5). In addition, EK-sup could promote the differentiation of basophil/mast cells (5). Latter cells, which are present in most tissues, play a pivotal role in allergic reactions via histamine, IL-3, and IL-4 release (6). The above data, however, did not provide clear-cut demonstration

of IL-3 presence in normal EK cultures. To answer this point, we investigated the *in situ* presence of IL-3-coding mRNA in EK. We have also assayed the ability of these cells to express and secrete CD23 (7). Indeed, soluble CD23 (sCD23) was recently shown to promote the generation of basophil-containing colonies from IL-1-stimulated, human CD34<sup>+</sup> bone marrow precursor cells (8). This molecule displays various other cytokine-like activities and is also known as the low affinity receptor for IgE (FcεRII, reviewed in 7). In addition, thymic epithelial cell cultures were recently shown to express CD23 and IL-3 (9, 10). The present work shows that EK express mRNA for both IL-3 and sCD23 and secrete these cytokines after appropriate activation. The involvement of these factors in basophil promoting activity of EK-sup was also demonstrated.

### Methods

**Epidermal cell cultures.** Keratinocytes were obtained from skin of several patients undergoing mastectomy for breast cancer, with their informed consent. Cells were grown from explants as described in detail elsewhere (9, 10). Briefly, the skin was cut into small pieces and incubated in medium containing penicillin, streptomycin, and amphotericin B (see below) for 1 h, then washed three times. 10 explants of 1 mm<sup>2</sup> were then anchored onto 25-cm<sup>2</sup> plastic flasks (Becton Dickinson, Plymouth, UK) for 3 h at 37°C. 4 ml of medium was added thereafter and changed every 3-4 d. Culture medium used in this work was McCoy's (Flow Laboratories, Irvine, UK) supplemented with 10% FCS (Institut Jacques Boy, Reims, France), 100 U/ml penicillin, 100 µg/ml streptomycin, 2.5 µg/ml amphotericin-B, 0.4 µg/ml hydrocortisone, 20 ng/ml epidermal growth factor, and/or 10<sup>-7</sup> M cholera toxin (all from Sigma Chemical Co., St. Louis, MO). EK were also obtained by another well-described culture method using serum-free MCDP medium (Gibco BRL, Cergy Pontoise, France) and irradiated 3T3 cell line as underlayer (11). The cells were grown to confluence, trypsinized thereafter (trypsin; Sigma Chemical Co.), counted, and resuspended in 24-well plates (Becton Dickinson) at 10<sup>6</sup>/ml. Only EK preparations with > 94% cytokeratin<sup>+</sup> cells were used in our work. They were then incubated in medium alone or with recombinant IL-1 (rIL-1), rIL-3, rIL-4, rGM-CSF (Genzyme Corp., Cambridge, MA), IFNα (Hoffman LaRoche, Basel, Switzerland), hydrocortisone, and/or cholera toxin (Sigma Chemical Co.). After 48-h incubation, EK-sup were collected and assayed for their biological activities. As a negative control, we have used supernatants from autologous fibroblasts (Fibro-sup) or 3T3 cells incubated in the same conditions. Skin fibroblasts were obtained from explants following culture method described in details elsewhere (9).

**Cell markers.** To control the purity of EK preparations, these cells were analyzed for their markers. For immunolabeling, EK were fixed on slides with 4% paraformaldehyde, then with acetone (at -20°C), and stained using the following mAb: KL1 (antikeratin), IOT11 (CD2), IOT6 (CD1a), IOT2a (HLA-DR) (Immunotech, Marseille, France), antivimentin (Amersham International, Amersham, UK). Reactivity of these mAb was visualized by indirect immunofluorescence. Furthermore, to control the possible contamination by melano-

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1. *Abbreviations used in this paper:* EK, epidermal keratinocytes; EK-sup, EK-derived supernatants; Fibro-sup, supernatants from autologous fibroblasts; GM-CSF, granulocyte macrophage colony-stimulating factor; rIL, recombinant IL; sCD23, soluble CD23.

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cytes we also performed DOPA (3,4 dihydroxy-L-phenylalanin) reaction on EK cells as described (12). These studies confirm EK nature of cultured cells as > 94% (range 94–99%) of the cells were cytokeratin<sup>+</sup> with < 1% contaminant CD1<sup>+</sup>, DR<sup>+</sup> (Langerhans cells) (14), CD2<sup>+</sup> (T cells), and/or DOPA-reactive (melanocytes) (13) cells. Only 1–2% of the cells expressed vimentin (fibroblasts); this small number of fibroblasts was not detected in EK co-cultured with 3T3 cells. By contrast, cells from fibroblast cultures were mainly vimentin<sup>+</sup> and cytokeratin<sup>−</sup>.

**Colony-forming unit assays.** Normal human bone marrow was obtained from patients undergoing hip replacement or from normal transplantation donors with their consent. Mononuclear cells were isolated on Ficoll-Hypaque gradient and myeloid precursors were then enriched by adherent and CD2<sup>+</sup> cell elimination (8). They were subsequently cultured (10<sup>5</sup>/ml) in collagen gel as described (8) using Iscove's modified Dulbecco's medium (Sigma Chemical Co.), containing 20% FCS and 1% desionized BSA (Fraction V; Sigma Chemical Co.). Cultures were also supplemented with various EK-sup or Fibro-sup at 20% final volume, rIL-1, rIL-3, rGM-CSF (Genzyme Corp.), rsCD23 (25-kD form; a gift of Dr. H. Hofstetter, Ciba-Geigy, Basel, Switzerland) (13), anti-IL-3, -IL-1, -IL-4 MAb (Genzyme Corp.), anti-CD25 and/or anti-CD23 mAb (IOT16 and IOB8; Immunotech, Marseille, France). Typical myeloid colonies (> 50 cell aggregates) were scored at day 10. Thereafter, collagen gels were transferred onto glass slides, air dried, and stained with May-Grünwald Giemsa (8) for cytological analysis.

**Northern blot analysis.** RNA was isolated from 2–4 × 10<sup>7</sup> EK by the guanidine isothiocyanate method (15). As IL-3-positive control, we used RNA from peripheral blood CD2<sup>+</sup> lymphocytes, isolated by sheep red blood cell reaction (8) and activated 18 h in RPMI 1640 medium containing 10% FCS and 100 µg/ml PHA-M (Sigma Chemical Co.). As CD23-positive control, we used EBV<sup>+</sup>, HC12P B cell lines that constitutively express CD23. IL-3 and CD23 oligonucleotide probes were labeled with <sup>32</sup>P by random priming (15). Hybridization and autoradiography were performed according to Sambrook et al. (15). For hybridization, a 500-bp gibbon IL-3 cDNA (XHO-XHO sites, kindly given by Dr. S. C. Clark, Genetics Institute, Cambridge, MA) and a 700-bp CD23-cDNA (BamHI-Pst sites, kindly given by Dr. H. Hofstetter, Ciba Geigy, Basel, Switzerland) (13) were used.

**In situ hybridization.** EK cultures were trypsinized, suspended, and cytocentrifuged at 5.10<sup>5</sup>/slide. The slides were then prehybridized for 2

h at 37°C in 50% desionized formamide-containing Denhardt's solution (Sigma Chemical Co.), 2 × standard saline citrate (SSC) yeast tRNA, and DTT (Boehringer Mannheim, Meylan, France). The cells were covered with 15 ml <sup>35</sup>S-labeled cDNA probe (2 × 10<sup>6</sup> cpm/slide) (9) in the prehybridizing solution and kept 16 h at 37°C. Thereafter, the slides were washed with formamide buffer, SSC (2 × 1 h at 55°C and 1 h at 22°C), dehydrated in ethanol ammonium acetate 0.3 M, air dried, and immersed in NTB2 Kodak emulsion (Eastman Kodak Co., Rochester, NY). Slides were developed six days later in Kodak D19 developer and fixed with 30% thiosulfate. They were also stained with Giemsa thereafter for better cell definition, and examined by light microscopy. As negative control, EK were also hybridized with CD8 probe or the PMX vector lacking IL-3 or CD23-specific cDNA.

**IL-3 and sCD23 assays.** IL-3 levels were quantified in EK-sup using IL-3 dependent, MO7 cell line (16). Soluble CD23 was kindly measured by Dr. G. Delespesse (Notre-Dame Hospital, Montreal, Canada) by a RIA detailed elsewhere (17).

## Results

**Generation of myeloid colonies in the presence of EK-supernatants.** Normal human bone marrow cells were seeded in semi-solid medium in the presence or the absence of EK-sup, Fibro-sup, rIL-1, rIL-3, rsCD23, and/or rGM-CSF. The colonies were scored at day 10 and subsequently analyzed for their cytologic aspect. Our data confirm previous observations which suggested the ability of EK-sup to sustain colony generation by human myeloid precursors (4, 5). EK-sup-induced colonies have typical multilineage morphology with some basophilic cells (Fig. 1). No such activity was observed in cells cultured with various Fibro-sup. The average of colonies obtained were 309 with 77 basophil-containing colonies (Table I). This activity is similar to that observed with 300 U/ml IL-3. Significant but lower activities were also observed in cells cultured with rGM-CSF or rIL-1 + rCD23. This confirms our early data (8) which showed that IL-1 pretreatment of myeloid precursors is a prerequisite for rsCD23 colony stimulating effect. In the ab-

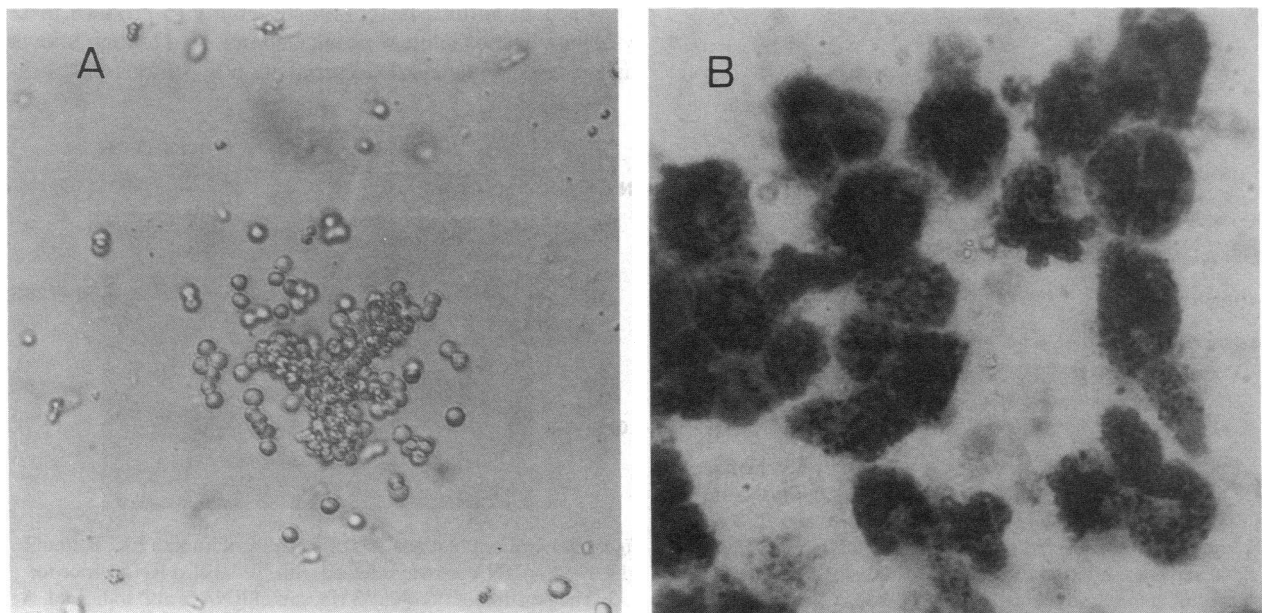


Figure 1. General aspect of (A) myeloid colonies induced by EK-sup and (B) cytological analysis of basophil-containing colonies (representative of results in Table I).

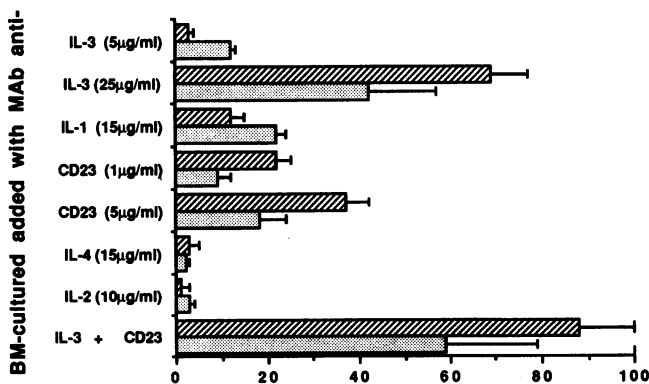
**Table I. Epidermal Keratinocytes Display Colony-stimulating and Basophil-promoting Activities**

Cultures supplemented with	Colonies/ $10^5$ cells	
	Total	Basophils+
Medium alone	2 $\pm$ 1	NT
EK-sup (20%)	309 $\pm$ 51	77 $\pm$ 9
Fibro-sup (20%)	2 $\pm$ 2	NT
3T3-sup (20%)	3 $\pm$ 2	NT
rIL-1 (50 U/ml)	5 $\pm$ 2	NT
rIL-3 (100 U/ml)	131 $\pm$ 27	42 $\pm$ 8
rIL-3 (300 U/ml)	329 $\pm$ 74	90 $\pm$ 16
rGM-CSF (100 U/ml)	164 $\pm$ 32	2 $\pm$ 2
rsCD23 (25 ng/ml)	5 $\pm$ 3	NT
rIL-1 + rsCD23	194 $\pm$ 28	54 $\pm$ 12
rIL-1 + rGM-CSF	171 $\pm$ 30	15 $\pm$ 3

Bone marrow cells were cultured in the presence of various factors and myeloid colonies scored at day 10. The cells were then stained with Giemsa and basophil-containing colonies scored. Results show mean $\pm$ SD of six experiments using three distinct marrow cell preparations and two different EK cell cultures. Each experiment was done in triplicate. (NT, not tested).

sence of rIL-1, rGM-CSF failed to significantly promote the differentiation of human basophils.

**Effect of various mAb on colony promotion by EK-sup.** The above data led us to assay the effect of neutralizing mAb to IL-1, IL-2, IL-3, IL-4, and CD23 on the number of total and basophil-containing colonies generated in the presence of EK-sup. Data in Fig. 2 show that upon addition of mAb to IL-3, CD23, or IL-1, colony numbers significantly decreased, while such inhibition was not observed with anti-IL-2, anti-IL-4, or CD25 mAb; the latter being an isotype-matched control for CD23 mAb. Thus, IL-4 used for EK-conditioning had no direct effect on marrow precursors. Interestingly, the number of

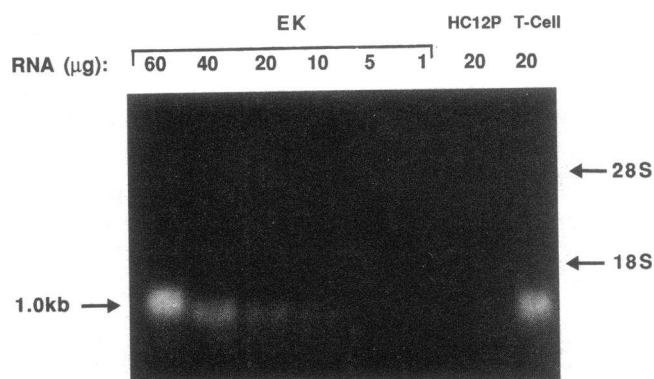


**Figure 2.** Effect of various mAb on colony generation by human bone marrow in the presence of EK-sup. mAb were added at optimal neutralizing dilutions (5–25  $\mu$ g/ml). When used together, anti-IL-3 and anti-CD23 mAb were added at 25  $\mu$ g/ml and 5  $\mu$ g/ml, respectively. Results show percent inhibition of myeloid or basophil-containing colonies (control colony numbers shown on Table I). Mean $\pm$ SD from three distinct cell preparations, each done in triplicates (SE < 15%). ▨, Percent inhibition of myeloid colonies; ■, percent inhibition of basophil-containing colonies.

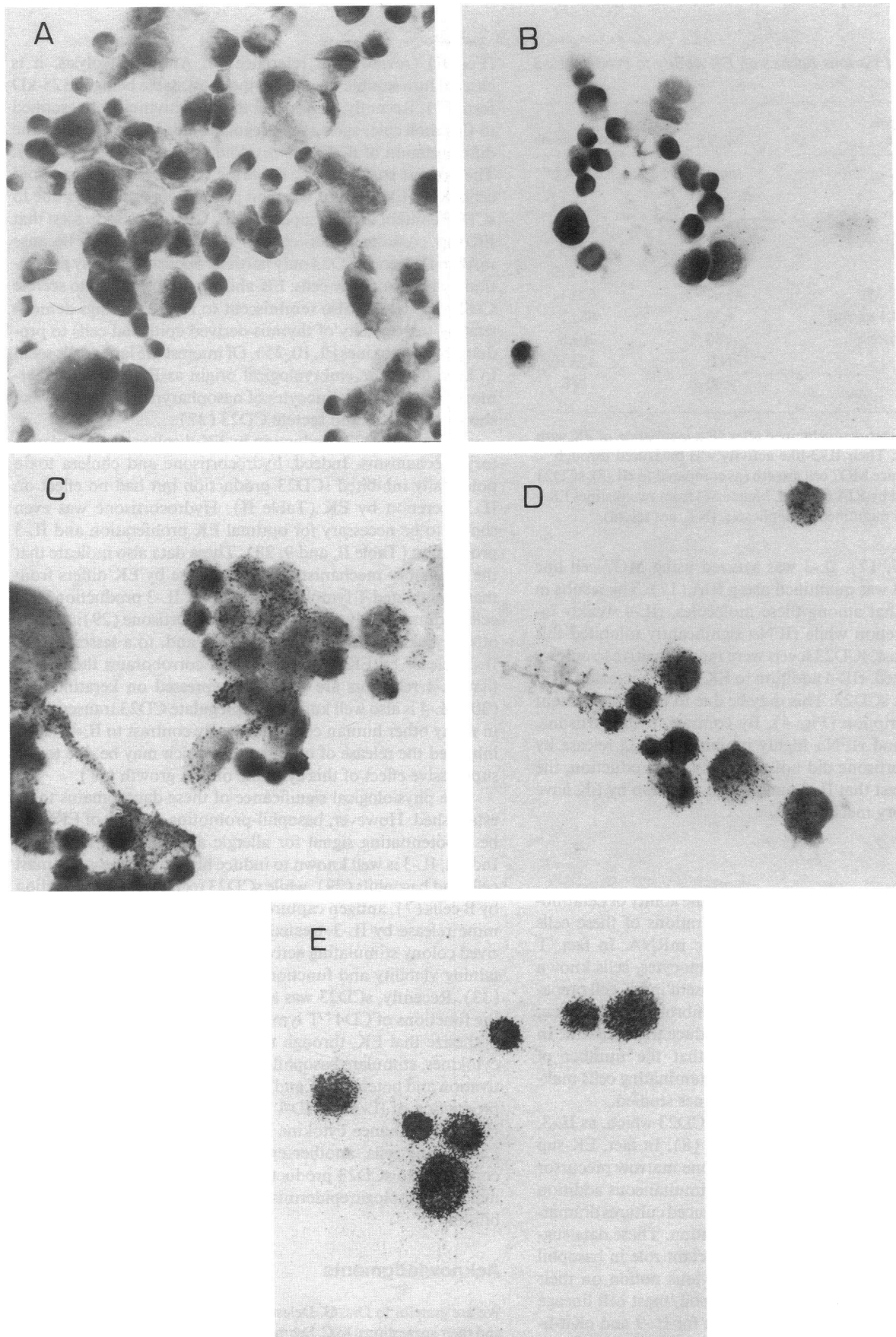
basophil-containing colonies were more affected by anti-IL-3 and CD23 mAb, as compared to total colonies. Furthermore, simultaneous addition of both mAb inhibited 88% basophilic colonies (compared to 59% inhibition of total colony numbers). This suggests that these factors are critical for basophil promotion by EK-sup. Finally, despite various mAb treatments, EK-sup still promoted significant colony numbers which could be due to the presence of other colony stimulating factors in EK-sup (3).

**IL-3 and CD23-specific RNA and mRNA revelation in EK.** The above data led us to investigate the presence of specific RNA for IL-3 and CD23 in EK. Indeed, although IL-3-like activity of normal human EK was widely documented (4, 5), no molecular approach was given to support these observations. Northern blot analysis of two distinct EK preparations shows that EK express a 1.0 kb long IL-3-RNA (represented in Fig. 3), therefore, apparently similar to activated T cell-derived IL-3 mRNA length. CD23-RNA of 1.7 kb was also detected from both EK and B cell line HC12P (not shown), which correlates with actual notion on mRNA expression in other human cells (7). No IL-3 RNA was detected in HC12P cells nor we observed CD23 expression by activated T cells. EK origin of these cytokines was further supported by in situ hybridization method permitting the detection of IL-3 and CD23 transcripts at a single cell level and the enumeration of positive cells. Five distinct EK preparations were analyzed and results of one EK population are represented on Fig. 4. Variations in mRNA levels were seen from one cell preparation to another which may be due to EK culture conditions (see below). However, IL-3-mRNA copies were generally found in higher intracellular density and in more cell numbers (73%) in EK as compared to CD23-mRNA expression (12%). After incubation with rIL-4, significantly higher CD23-mRNA<sup>+</sup> cell numbers (38%) were detected (Fig. 4), which suggest that IL-4 stimulates CD23 transcription in EK.

**Effect of various culture conditions on IL-3 and sCD23 production by EK.** In regard to the role of IL-3 and sCD23 on basophil-promoting activity of EK-sup, we subsequently tested the effects of various factors on EK ability to produce these cytokines. These factors were selected in regard to their known capacity to modulate sCD23 production by various CD23-ex-



**Figure 3.** Northern blot analysis of RNA from human EK, B, and T cells. 1–60  $\mu$ g RNA were hybridized with  $^{32}$ P-labeled RNA probe for IL-3. The position of 28S and 18S ribosomal RNA is also indicated. A 1.0-kb IL-3 transcript was observed in both EK- and activated T cell-derived RNA, but no IL-3 transcript was found in HC12P, B cell line. Results are of one representative experiment.



**Figure 4.** Expression of IL-3 and CD23-specific mRNA by human EK. (A) Unstained cells; (B) negative control: EK were hybridized with CD8 probe; (C) IL-3 and (D) CD23 mRNA expression by EK cultured in medium alone; (E) CD23-mRNA expression by EK after 48 h stimulation with IL-4.

Table II. Effect of Various Factors on EK Ability to Produce IL-3 and sCD23

EK-sup from cells cultured with	sCD23	MO-7 growth
	pg/ml	cpm $\times 10^3$
Medium	63 $\pm$ 10	63 $\pm$ 11
rIL-4 (100 U/ml)	412 $\pm$ 112	64 $\pm$ 1
rIFN $\alpha$ (500 U/ml)	<30	33 $\pm$ 5
rIL-4 + rIFN $\alpha$	71 $\pm$ 11	34 $\pm$ 10
Cholera toxin (10 $^{-7}$ M)	45 $\pm$ 7	62 $\pm$ 1
Hydrocortisone (0.4 $\mu$ g/ml)	<30	68 $\pm$ 2
rIL-4 + hydrocortisone	<30	70 $\pm$ 6
rIL-3 (300 U/ml)	NT	47 $\pm$ 10
Fibro-sup (20%)	<30	NT

EK-sup and Fibro-sup were obtained after 48 h incubation of EK with various cytokines. Their IL-3-like activity was measured through their ability to induce MO7 cell growth (as compared to rIL-3). sCD23 levels were assayed by RIA method. Mean $\pm$ SD from two distinct EK preparations, each quantified in duplicates. (NT, not tested).

pressing cells (7, 17). IL-3 was assayed using MO7 cell line (16) and sCD23 was quantified using RIA (17). The results in Table II show that among these molecules, rIL-4 weakly induced IL-3 secretion while rIFN $\alpha$  significantly inhibited this factor. By contrast, sCD23 levels were more sensitive to culture conditions. Indeed, rIL-4 addition to EK highly increased their ability to secrete sCD23. This may be due to the enhancement of CD23 transcription (Fig. 4). By contrast, hydrocortisone, cholera toxin, and rIFN $\alpha$  highly inhibited sCD23 release by EK. As hydrocortisone did not suppress IL-3 production, the above data suggest that IL-3 and sCD23 secretion by EK have distinct regulatory mechanisms.

## Discussion

The above data definitively demonstrate the ability of keratinocytes to produce IL-3 as purified preparations of these cells contained high amounts of IL-3 specific mRNA. In fact, T lymphocytes, Langerhans cells and melanocytes, cells known for their high secretory functions, were absent in EK cell preparations. Although 1–3% of contaminant fibroblasts were seen, these cells did not have the ability to produce this cytokine. In situ hybridization data also indicate that the number of mRNA $^+$  cells surpass the number of contaminating cells making unlikely non-EK origin of the cytokines studied.

Our data also show that EK secrete sCD23 which, as IL-3, displayed a basophil-promoting activity (8). In fact, EK-sup was able to induce the proliferation of bone marrow precursor cells in semisolid medium. Of interest, simultaneous addition of mAb to IL-3 and CD23 on EK-sup-induced cultures dramatically inhibited basophilic cell differentiation. These data suggest that IL-3 and sCD23 have an important role in basophil promotion by EK and corroborate previous notion on their specificity in the differentiation of basophil/mast cell lineage (Table I, and 8, 18, 19). Indeed, except for IL-9 and cKit-ligand (20, 21), most other known colony stimulating factors failed to sustain human basophil development.

CD23 is a surface antigen expressed by a variety of human cells and also known as the low affinity receptor for IgE

(Fc $\epsilon$ R2) (reviewed in reference 7). After proteolysis, it is cleaved into soluble fragments, the most stable being the 25-kD form (7). Recently, various biological activities were ascribed to this molecule, such as the regulation of IgE release and the differentiation of B, T, and myeloid precursors (7, 8, 22–24). The present study further confirms sCD23 effect on myeloid cells (8) as EK-derived basophil promotion was in part due to sCD23 content in their supernatants. Our data also suggest that EK-sup contains other colony stimulating factors because mAb to IL-3 and sCD23 only partially abolished colony generation by bone marrow cells. EK ability to express and to secrete CD23 and IL-3 is also reminiscent to recent findings demonstrating the capacity of thymus-derived epithelial cells to produce these cytokines (9, 10, 25). Of interest the latter cells seem to have the same embryological origin as EK (26). Furthermore, epithelial keratinocytes of nasopharynx carcinoma were shown to express and secrete CD23 (27).

IL-3 and sCD23 production by EK displays distinct regulatory mechanisms. Indeed, hydrocortisone and cholera toxin potentially inhibited sCD23 production but had no effect on IL-3 secretion by EK (Table II). Hydrocortisone was even shown to be necessary for optimal EK proliferation and IL-3 production (Table II, and 9, 28). These data also indicate that the regulatory mechanism of IL-3 release by EK differs from that of activated T lymphocytes. Indeed, IL-3 production by T cells is dramatically abolished by hydrocortisone (29). Among other cytokines, IL-4 induced sCD23 and, to a lesser extent, IL-3 release by EK. This IL-4 effect corroborates the notion that IL-4 receptors are generally expressed on keratinocytes (30). IL-4 is also well known to upregulate CD23 transcription in many other human cells (7, 17). By contrast to IL-4, IFN $\alpha$  inhibited the release of both factors, which may be due to the suppressive effect of this cytokine on EK growth (31).

The physiological significance of these data remains to be established. However, basophil-promoting activity of EK may be a potentiating signal for allergic and immune responses. Indeed, IL-3 is well known to induce histamine release by mast cells and basophils (29), while sCD23 regulates IgE production by B cells (7), antigen capture by IgE (22, 23), as well as histamine release by IL-3-treated human basophils (32). EK-derived colony stimulating activity may also play a role in maintaining viability and functions of epidermal Langerhans cells (33). Recently, sCD23 was also shown to selectively enhance the functions of CD4 $^+$  T lymphocytes (34). Therefore, we hypothesize that EK, through their capacity to secrete multiple cytokines, stimulate basophil/mast cell differentiation and activation and potentiate T and mast cell functions, including the production of IL-3 and IL-4 by these cells (6). Consequently, IL-4 may enhance cytokine production by EK as well as by Langerhans cells, another epidermis constituent which may contribute to sCD23 production (14). In situ studies on normal and pathologic epidermis are needed to answer these possibilities.

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