Cell-specific Induction of Distinct Oncogenes of the Jun Family Is Responsible for Differential Regulation of Collagenase Gene Expression by Transforming Growth Factor-β in Fibroblasts and Keratinocytes

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Transforming growth factor-β (TGF-β) plays a major role in regulating connective tissue deposition by controlling both extracellular matrix production and degradation. In this study, we show that TGF-β transcriptionally represses both basal and tumor necrosis factor-α-induced collagenase (matrix metalloproteinase-1) gene expression in dermal fibroblasts in culture, whereas it activates its expression in epidermal keratinocytes. We demonstrate that this differential effect of TGF-β on collagenase gene expression is due to a cell type-specific induction of distinct oncogenes of the Jun family, which participate in the formation of AP-1 complexes with different trans-activating properties. Specifically, our data indicate that the inhibitory effect of TGF-β in fibroblasts is likely to be mediated by jun-B, based on the following observations: (a) TGF-β induces high levels of jun-B expression and (b) over-expression of jun-B mimics TGF-β effect in inhibiting basal collagenase promoter activity and preventing tumor necrosis factor-α-induced trans-activation of the collagenase promoter. In contrast, TGF-β induction of collagenase gene expression in keratinocytes is preceded by transient elevation of c-jun proto-oncogene expression. Over-expression of c-jun leads to trans-activation of the collagenase promoter in both cell types, suggesting that c-jun is an ubiquitous inducer of collagenase gene expression. Transfection of keratinocytes with an antisense c-jun construct together with a collagenase promoter/reporter gene construct inhibits basal and TGF-β-induced up-regulation of the collagenase promoter activity, implying that c-jun mediates TGF-β effect in this cell type. Collectively, our data suggest differential signaling pathways for TGF-β in dermal fibroblasts and epidermal keratinocytes, leading to cell type-specific induction of two AP-1 components with opposite transcriptional activities.

Matrix metalloproteases comprise a family of proteolytic enzymes involved in the degradation of the extracellular matrix of connective tissue (for reviews see Refs. 1 and 2). These enzymes play a critical role in a number of physiological and pathological processes involving connective tissue remodeling and/or destruction, as exemplified by embryonic development, wound repair, tumor metastasis, and rheumatoid arthritis. Breakdown of the fibrillar collagen network is initiated by interstitial collagenase (matrix metalloproteinase-1), whereas the other components of the matrix are degraded primarily by stromelysins and gelatinases.

The expression of matrix metalloproteases by connective tissue cells is modulated by a variety of cytokines and growth factors (2). In particular, interleukin-1 and tumor necrosis factor-α (TNF-α) are potent activators of fibroblast collagenase gene expression, and their effect is mediated by c-jun, the product of the c-jun proto-oncogene, which participates in the formation of the transcription factor AP-1 (1, 2). In contrast, transforming growth factor-β (TGF-β) has been shown to inhibit fibroblast collagenase gene expression through Jun-B-dependent mechanisms (3), whereas it inhibits the expression of transin, the rat homologue of stromelysin, through Fos-mediated mechanisms (4).

Recent in vivo observations have revealed that during cutaneous wound healing, the expression of collagenase is very low in the dermis, whereas it is markedly elevated in basal keratinocytes at the wound edges (5). In this context, the close topographic proximity of fibroblasts and keratinocytes led us to investigate in vitro the signals that would be responsible for the differential, cell type-specific expression of collagenase during wound healing. We report that TGF-β, a growth factor with essential wound healing promoting activities (6–9), is a potent inhibitor of collagenase gene expression in fibroblasts, whereas it strongly up-regulates collagenase expression in keratinocytes. We demonstrate that cell-specific induction of different oncogenes of the Jun family, with opposite trans-activating properties, is responsible for the differential regulation of collagenase gene expression by TGF-β in fibroblasts and keratinocytes.

MATERIALS AND METHODS

Cell Cultures—Human dermal fibroblast cultures, established by explanting tissue specimens obtained from neonatal foreskins, were utilized in passages 3–8. The cells were maintained in Dulbecco’s modified Eagle’s medium (DMEM) supplemented with 10% fetal calf serum, 2 mM glutamine, and antibiotics (50 μg/ml streptomycin, 200 units/ml penicillin, and 100 μg/ml amphotericin B).

The abbreviations used are: TNF-α, tumor necrosis factor-α; DMEM, Dulbecco’s modified Eagle’s medium; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; KGM, keratinocyte growth medium; TGF-β, transforming growth factor-β; CAT, chloramphenicol acetyltransferase; PCR, polymerase chain reaction; RSV, Rous sarcoma virus; TRE, TPA response element.

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penicillin-G, 0.25 μg/ml, Fungizone (g). One hour prior to the addition of growth factors, the confluent fibroblast cultures were rinsed with DMEM and placed in DMEM containing 1% fetal calf serum.

Human epidermal keratinocytes obtained by explanting foreskin specimens, were grown in serum-free, low calcium (0.15 mM), keratinocyte growth medium supplemented with epidermal growth factor, hydrocortisone, insulin, and bovine pituitary extract (KGM, Clonetics Corp., San Diego, CA), and utilized in passage 1 to avoid differentiation inherent to subculturing of these cells. One hour prior to the experiments, the confluent keratinocyte cultures were placed in fresh KGM.

Cytokines/Growth Factors—Human recombinant TGF-β was a generous gift from Dr. David R. Olsen (Celtrix Laboratories, Santa Clara, CA). Human recombinant TNF-α was purchased from Boehinger Mannheim.

Northern Analyses—At the end of incubation with growth factors, cell cultures were subjected to isolation of total RNA as described previously (10). RNA was fractionated in 0.8% agarose gels containing formaldehyde and analyzed by Northern hybridization with ^32P-labeled cDNA probes (11). The [^32P]cDNA-mRNA hybrids were visualized by autoradiography, and the steady-state levels of mRNA were quantitated by scanning densitometry using a He-Ne laser scanner at 633 nm (LKB Produkter, Bromma, Sweden).

cDNAs and Plasmid Constructs—The following cDNAs were used for Northern hybridizations to detect specific mRNA transcripts: a 2.0-kilobase pair human collagenase cDNA (12), a gift from Dr. Gregory J. Goldberg (Washington University School of Medicine, St. Louis, MO) and a rat glyceraldehyde-3-phosphate dehydrogenase (GAPDH) cDNA was used in control hybridizations to normalize for differences in the loading and transfer of RNA (13). For c-jun, we used a full-length human cDNA in pRSVe expression vector (14); and for jun-B, a full-length cDNA in pRSVe expression vector (14), both kindly provided by Dr. Michael Karin (UCSD, La Jolla, CA).

To study the transcriptional regulation of collagenase gene expression, the following plasmid construct was used in transient transfection experiments: pCLCAT3, which contains −3.8 kilobase pairs of 5′-flanking DNA of human collagenase gene linked to the CAT reporter gene (15), kindly provided by Dr. Steven M. Frisch (La Jolla Cancer Research Foundation, La Jolla, CA). The oncogene expression vectors described above were used in co-transfection experiments. Empty pRSVe was used as filling plasmid in order to transfect the same amount of DNA in every plate.

To prepare an antisense c-jun construct, a fragment spanning the region +451 to +617 of the c-jun gene was amplified by polymerase chain reaction (PCR). The PCR amplimers were cloned into a plasmid vector (InVitrogen Corp., San Diego, CA), and the clones containing the insert were sequenced to ensure the fidelity of the PCR amplification. The PCR products were then inserted into a plasmid vector (pRSVe-NIH3T3) kindly provided by Dr. Gregory I. Goldberg (Washington University School of Medicine, St. Louis, MO) and used as filling plasmid in order to transfect the same amount of DNA in every plate.

FIG. 1. Effect of TGF-β on collagenase gene expression in dermal fibroblasts. Confluent fibroblast cultures were incubated in medium containing 1% fetal calf serum without (−) or with (+) TNF-α (10 ng/ml), in the absence (−) or the presence (+) of TGF-β (10 ng/ml). After 24 h, total RNA was extracted and analyzed by Northern hybridization with a collagenase-specific cDNA; a GAPDH cDNA was used as a control. A, autoradiograms. B, densitometric analysis after correction for GAPDH mRNA levels.

RESULTS

Cell Type-specific Effect of TGF-β on Collagenase Gene Expression—In the first set of experiments, human adult skin fibroblasts were incubated for 24 h without or with TGF-β or TNF-α, both at a concentration of 10 ng/ml. At the end of incubation, RNA was extracted and analyzed for collagenase gene expression by Northern hybridization. Visual observation of the autoradiograms indicated that TGF-β markedly down-regulated both basal and TNF-α-induced elevation of collagenase mRNA steady-state levels in parallel fibroblast cultures (Fig. 1A). Quantitation of the autoradiograms by scanning densitometry and correction against GAPDH mRNA levels in the corresponding RNA preparations indicated that the expression of collagenase in TGF-β-treated cultures was reduced by ~80% in comparison with control fibroblast cultures. TNF-α enhanced collagenase mRNA levels by ~6-fold, but in cultures treated concomitantly with TNF-α and TGF-β, the levels were reduced by ~75% in comparison with cultures treated with TNF-α alone (Fig. 1B).

In the second set of experiments, confluent keratinocyte cultures were incubated for 24 h without or with TGF-β and/or TNF-α at concentrations of either 1 or 10 ng/ml. Contrasting with its inhibitory effect observed in dermal fibroblasts, TGF-β was found to be a potent enhancer of keratinocyte collagenase gene expression (Fig. 2, second and third lanes). On the other hand, TNF-α, which is a potent enhancer of collagenase gene expression in fibroblasts (see Fig. 1), had little effect on the basal expression of collagenase in keratinocytes (Fig. 2, fifth
and sixth lanes) and a minimal effect on the induction exerted by TGF-β (Fig. 2, fourth lane). Quantitation of the autoradiograms after normalization of collagenase mRNA levels against those of GAPDH showed a 4.5–5-fold elevation of collagenase mRNA steady-state levels upon TGF-β stimulation, whereas TNF-α did not stimulate collagenase expression (Fig. 2B).

Additional experiments with various concentrations (0.1, 1, and 10 ng/ml) of TGF-β indicated a stimulatory effect with as little as 0.1 ng/ml (−2.8-fold); whereas maximal elevation of collagenase mRNA levels (−6-fold) was observed with 1 ng/ml of TGF-β, no further enhancement was noted with 10 ng/ml of TGF-β (not shown).

Transient cell transfections with a collagenase promoter/CAT reporter gene construct were performed to examine whether TGF-β regulates collagenase mRNA steady-state levels through modulation of transcript at the promoter level. Human neonatal fibroblasts were transfected with the collagenase promoter/CAT construct pCLCAT3 and treated with TGF-β or TNF-α at 10 ng/ml concentration. Assay of CAT activity after 40 h of incubation indicated that TGF-β reduced the promoter activity by 40–60%, as compared with that of control cultures (Fig. 3). Also TGF-β counteracted TNF-α-induced elevation of the collagenase promoter activity.

In another set of experiments, confluent keratinocyte cultures in serum-free KGM were incubated for 24 h in the absence or presence of TGF-β. Confluent keratinocyte cultures in serum-free KGM were incubated for 24 h in the absence or presence of TGF-β, and assays of CAT activity were performed to examine the promoter activity by 40–60%, as compared with that of control cultures (Fig. 3). Also TGF-β counteracted TNF-α-induced elevation of the collagenase promoter activity.

B Autoradiograms. B, densitometric analysis after correction for GAPDH mRNA levels.
Fig. 4. Effect of TGF-β on collagenase promoter activity in epidermal keratinocytes. Confluent keratinocyte cultures in serum-free KGM were transfected with pCLCAT3 using a liposome-based method (DOTAP, Boehringer Mannheim) according to the manufacturer’s protocol. Five hours after transfections, the medium was replaced with fresh KGM and TGF-β in various concentrations was added 2 h later for a 48-h incubation. CAT activity, representing collagenase promoter activity, was determined. The results, presented as relative promoter activity, are the means ± S.D. of three independent experiments run with duplicate samples and expressed as fold induction over the controls, which are set as 1.0.

Fig. 5. Effect of TNF-α and TGF-β on c-jun and jun-B gene expression in dermal fibroblasts. Confluent fibroblast cultures were incubated in medium containing 1% fetal calf serum without (CTRL) or with TNF-α (10 ng/ml), in the absence (−) or the presence (+) of TGF-β (10 ng/ml). Total RNA was extracted after 0, 1, or 6 h of incubation and analyzed by Northern hybridizations with 32P-labeled cDNA probes specific for c-jun and jun-B mRNAs. A GAPDH cDNA was used as a control.

Fig. 6. Effect of TGF-β on the ratio of c-jun/jun-B mRNA in dermal fibroblasts. Relative c-jun and jun-B mRNA levels were determined in each RNA preparation by densitometric analysis of the autoradiograms shown in Fig. 5. Raw values were corrected for GAPDH mRNA levels in the same RNA preparations and for the specific activity of the c-jun and jun-B probes. The ratio of c-jun and jun-B mRNA levels was calculated for the various time points of cytokine treatment. Open squares, control; solid squares, TGF-β; open triangles, TNF-α; solid triangles, TNF-α + TGF-β.

Expression of c-jun in fibroblasts was very low and, although expression was enhanced after 1 h of incubation with TGF-β, it remained well below the level of expression of c-jun. In fact, using 32P-labeled cDNA probes with similar specific activities (−2 × 107 cpm/μg), a 48-h exposure of the autoradiograms was necessary to detect the low jun-B expression, whereas a 14-h exposure was sufficient to easily detect c-jun expression (Fig. 7). Therefore, in keratinocytes, after TGF-β stimulation, the ratio c-jun/jun-B is largely in favor of c-jun, ~25-fold more c-jun mRNA than jun-B at 1 h after addition of TGF-β, as estimated by scanning densitometry of the autoradiograms, correction for GAPDH mRNA levels in the RNA preparations, and differences in the exposure times of the autoradiograms. These data contrast the reverse situation observed in dermal fibroblasts in which jun-B expression is boosted by TGF-β treatment (see above, Figs. 5 and 6). It should be noted that the extent of stimulation of collagenase gene expression as detected at the mRNA level (~15-fold after 6 h) was more pronounced than the induction of promoter activity observed in transient cell transfection experiments (see Fig. 4). It is conceivable that TGF-β, in addition to activating the collagenase promoter, may also increase collagenase gene expression by post-transcriptional mechanisms such as stabili-
were then treated for 6 h with either TNF-α or TGF-β. The confluent fibroblast cultures were grown to confluency. Three hours prior to the addition of growth factors, the confluent fibroblast cultures were rinsed with DMEM and placed in DMEM containing 1% fetal calf serum. Total RNA was extracted and analyzed by Northern hybridization with 32P-labeled cDNA probes for collagenase, c-jun and jun-B. A GAPDH cDNA was used as a control.

Characterization of the Antisense Activity of pRSV-ASc-jun—In order to verify the activity of the pRSV-ASc-jun antisense construct, pRSVεNIH3T3 and pRSV-ASc-junNIH3T3 fibroblast cultures were grown to confluency. Three hours prior to the addition of growth factors, the confluent fibroblast cultures were rinsed with DMEM and placed in DMEM containing 1% fetal calf serum. The cultures were then treated for 6 h with either TNF-α or TGF-β, each at a concentration of 10 ng/ml. Total RNA was extracted and analyzed by Northern hybridization with 32P-labeled cDNA probes for collagenase, c-jun and jun-B. A GAPDH cDNA was used as a control.

In view of the data described above, it appears that in both cell types studied, enhanced expression of c-jun occurs in response to TGF-β, but not TNF-α. Furthermore, c-jun expression is stimulated approximately 6- to 8-fold in fibroblasts and 2- to 4-fold in keratinocytes. For this purpose, pCLCAT3 was co-transfected with either an RSV/ c-jun expression vector or an empty RSV vector as a control. Over-expression of c-jun in both fibroblasts and keratinocytes led to trans-activation of the collagenase promoter, as reflected by measurement of CAT activity in the different cell extracts. The extent of stimulation of each collagenase promoter was similar in both cell types: 5.3 ± 0.7-fold (n = 8) in fibroblasts versus 4.9 ± 0.9-fold (n = 6) in keratinocytes. In contrast, over-expression of jun-B resulted in reduced collagenase promoter activity in both cell types (not shown), attesting to the specificity of the expression vectors, as expected from previous observations by us and others (3, 14).

Characterization of the Antisense Activity of pRSV-ASc-jun—Control (pRSVεNIH3T3) and pRSV-ASc-junNIH3T3 fibroblast cultures (see "Materials and Methods") were grown to confluency. Three hours prior to the addition of growth factors, the confluent fibroblast cultures were rinsed with DMEM and placed in DMEM containing 1% fetal calf serum. The cultures were then treated for 6 h with either TNF-α or TGF-β, both at a concentration of 10 ng/ml, prior to Northern analysis. As shown in Fig. 8, significant expression of both c-jun and jun-B was noted in unstimulated pRSVεNIH3T3 cultures (lane 1). TNF-α strongly elevated c-jun expression, and jun-B to a lesser extent (lane 2). TGF-β slightly elevated jun-B expression but had no effect on c-jun mRNA levels (lane 3). pRSV-ASc-junNIH3T3 cultures showed very little basal expression of c-jun (lanes 4), about 7% of that observed in control cultures, as measured by scanning densitometry and after correction for GAPDH mRNA levels in the same RNA preparations, whereas

DISCUSSION

Several studies have shown differences in the pattern of expression and response to extracellular stimuli between c-jun and jun-B in a variety of experimental systems (3, 22–24). Furthermore, considerable differences in their trans-activation and transforming activities have been reported (3, 14, 25, 26). For example, whereas c-jun is an efficient activator of the c-jun and collagenase promoters that contain a single TRE, J un-B is not. In addition, J un-B counteracts activation of these promoters by c-jun. However, like c-jun, J un-B is a potent activator of
Cell-specific Regulation of Gene Expression by TGF-β

TGF-β has been shown to reduce collagenase gene expression and activity in cultured fibroblasts. This inhibition results from two distinct mechanisms: (a) TGF-β reduces the expression of the collagenase gene and (b) the expression of tissue inhibitor of metalloproteases is elevated by TGF-β (31). Our data indicate that the concept of TGF-β as a potent inhibitor of matrix remodeling is cell type-specific because this growth factor is a potent activator of collagenase gene expression in epidermal keratinocytes in culture. In that respect, TGF-β has been shown previously to up-regulate both 92- and 72-kDa gelatinase activity and gene expression in both fibroblasts and keratinocytes (32, 33).

Recently, it has been demonstrated using in situ hybridization in ulcerative skin lesions such as pyogenic granulomas that collagenase is expressed near the advancing edge of the ulceration, within the disrupted epidermis adjacent to an ulcer (5). By contrast, no hybridization signal was detected within the dermis or normal, intact epidermis. Therefore, basal keratinocytes seem to be the primary source of collagenase during wound healing, suggesting that keratinocytes play an essential role in tissue remodeling. It has been suggested that the signals that activate collagenase in keratinocytes are provided by the dermal extracellular matrix. In agreement with this hypothesis is the fact that keratinocytes grown on type I collagen exhibit enhanced collagenase production (34). By contrast, activation of fibroblast collagenase expression may be mediated by soluble factors such as interleukin-1 or TNF-α, rather than by the extracellular matrix. Skin injury is accompanied by release of interleukin-1, which in turn may activate fibroblasts but not keratinocytes to produce collagenase (34). Our data provide an alternative model for the cell-specific activation of collagenase gene expression during wound healing in which TGF-β, which is present in abundant amounts in the healing wound bed, could simultaneously turn off the expression of collagenase in fibroblasts while activating that of keratinocytes directly in contact with the dermis. We hypothesize that collagenase-secreting keratinocytes, possibly in response to TGF-β, may be able to migrate to dose the wound. This hypothesis is supported indirectly by a previous study indicating that TGF-β stimulates the outgrowth of epidermal cells from skin explant cultures (35).

In conclusion, this study has provided the first evidence for cell type-specific, differential induction of two transcription factors of the same family with antagonist trans-activation properties, leading to opposite regulation of collagenase gene expression in fibroblasts and keratinocytes by TGF-β.

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REFERENCES

1. Woessner, J. F., Jr. (1991) J. Biol. Chem. 5, 2145–2154
2. Mauviel, A. (1993) J. Biol. Chem. 5, 289–296
3. Mauviel, A., Chen, Y. Q., Dong, W., Evans, C. H., and Uitto, J. (1993) Curr. Biol. 3, 822–831
4. Kerr, L. D., Miller, D. B., and Matrisian, L. M. (1990) Cell 61, 267–278
5. Sairaalho-Kere, U., Chang, E. S., Welgus, H. G., and Parks, W. C. (1992) J. Clin. Invest. 90, 1952–1957
6. Barnard, J. A., Lyons, R. M., and Moses, H. L. (1990) Biochim. Biophys. Acta 1032, 79–87
7. Massagué, J. (1990) Annu. Rev. Cell Biol. 6, 579–641
8. Roberts, A. B., and Sporn, M. B. (1990) in Peptide Growth Factors and Their Receptors (Sporn, M. B., and Roberts, A. B., eds) pp. 419–472, Springer-Verlag New York, Inc., New York
9. Wahl, S. M. (1992) J. Clin. Immunol. 12, 61–74
10. Chomczynski, P., and Sacchi, N. (1987) Anal. Biochem. 162, 156–159
11. Sukorok, J., Fritsch, E. F., and Maniatis, T. (1989) Molecular Cloning: A Laboratory Manual, Second Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY
12. Goldberg, G. I., Wilhème, S. M., Kronberger, A., Bauer, E. A., Grant, G. A., and Eisen, A. Z. (1986) J. Biol. Chem. 261, 6600–6605
13. Fort, P., Marty, L., Piechaczek, M., El Sabrouty, S., Danz, C., Janteur, P., and Blanchard, J.-M. (1985) Nucleic Acids Res. 13, 1431–1442
14. Chiu, R., Angel, P., and Karin, M. (1989) Cell 59, 979–986
15. Frisch, S. M., Reich, R., Collier, J. E., Genrich, L. T., Martin, G., and Goldberg, G. I. (1990) Oncogene 5, 75–83
16. Graham, F., and Van der Eb, A. (1973) Virology 52, 456–457
17. Gorman, C. M., Moffat, L. F., Howard, B. H. (1982) Mol. Cell. Biol. 2, 1044–1051
18. Brenner, D. A., O’Hara, M., Angel, P., Chojkier, M., and Karin, M. (1989) Nature 337, 661–663
19. Conca, W., Kaplan, P. B., and Krane, S. M. (1989) J. Clin. Invest. 83, 1753–1757
20. Brinckerhoff, C. E., Plucinska, I. M., Sheldon, L. A., and O’Connor, G. T. (1986) Biochemistry 25, 6378–6384
21. Delany, A. M., and Brinckerhoff, C. E. (1992) J. Cell Biochem. 50, 400–410
22. Bartel, D., Sheng, M., Lau, L., and Greenberg, M. (1989) Genes & Dev. 3, 304–313
23. Pertovaara, L., Sistonen, L., Bos, T., Vogt, P., Keski-Oja, J. , and Alitalo, K. (1989) Mol. Cell. Biol. 9, 1255–1262
24. Wilkinson, D. G., Bhatt, S., Ryseck, R. P., and Bravo, R. (1989) Development 106, 465–471
25. Schütte, J., Viallet, J., Nau, M., Segal, S., Fedorko, J., and Minna, J. (1989) Cell 59, 987–997
26. Ryseck, R. P., and Bravo, R. (1991) Oncogene 6, 533–542
27. Deng, T., and Karin, M. (1993) Genes & Dev. 7, 479–490
28. Hirai, S., Ryseck, R. P., Mochita, F., Bravo, R., and Yaniv, M. (1989) EMBO J. 8, 1433–1438
29. Meliström, B., Achaval, M., Montero, D., Navanjo, J. R., and Sassone-Corsi, P. (1991) Oncogene 6, 1599–1604
30. Bossy-Wetzel, E., Bravo, R., and Hanahan, D. (1992) Genes & Dev. 6, 2340–2351
31. Edwards, D. R., Murphy, G., Reynolds, J. J., Whitham, S. E., Docherty, A. J. P., Angel, P., and Heath, J. K. (1987) EMBO J. 6, 1899–1904
32. Overall, C. M., Wrana, J. L., and Sodek, J. (1991) J. Biol. Chem. 266, 14064–14071
33. Salo, T., Lyons, J. G., Rahemtulla, F., Birkedal-Hansen, H., and Larjava, H. (1991) J. Biol. Chem. 266, 11436–11441
34. Petersen, M. J., Woodley, D. T., Stricklin, G. P., and O’Keefe, E. J. (1990) J. Invest. Dermatol. 97, 341–346
35. Hebd, P. (1988) J. Invest. Dermatol. 91, 440–445
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