Differential Regulation of Decorin and Biglycan Gene Expression by Dexamethasone and Retinoic Acid in Cultured Human Skin Fibroblasts

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Proteoglycans participate in the assembly of extracellular matrix, directly by interacting with other matrix components and indirectly by regulating cellular growth-factor responses. We have studied the regulation of gene expression of two small extracellular matrix chondroitin/dermatan sulfate proteoglycans, decorin and biglycan, by dexamethasone and retinoic acid in cultured human skin fibroblasts. Dexamethasone increased decorin production, maximally 4.8-fold, and decorin mRNA levels up to 2.3-fold, but had no effect on biglycan production or mRNA levels. Dexamethasone also prevented transforming growth factor-β–elicited down-regulation of decorin mRNA levels and production by dermal fibroblasts. In addition, dexamethasone potently inhibited enhancement of biglycan production and mRNA levels by transforming growth factor-β. Retinoic acid dose dependently reduced decorin mRNA levels (by 51%) and production (by 72%), but had no effect on biglycan gene expression. Retinoic acid did not alter the effect of transforming growth factor-β on decorin or biglycan production or mRNA levels. These results provide evidence that the effects of glucocorticoids and retinoids on dermal connective tissue are partially mediated via altered expression of decorin and biglycan, which both in turn regulate the activity of transforming growth factor-β, the most potent stimulator of connective tissue deposition. ***Key words: glucocorticoid/proteoglycan/extracellular matrix/transforming growth factor-β. J Invest Dermatol 104:503–508, 1995***

Proteoglycans are integral components of the extracellular matrix of dermal connective tissue. They participate in the assembly of extracellular matrix by interacting with other matrix components including collagens, fibronectin, elastic fibers, and hyaluronan [1–3]. Recently, cloning of cDNAs for core proteins of several extracellular matrix proteoglycans has revealed the detailed structure of these macromolecules and has helped elucidate their functions [1–3]. Specifically, the core proteins of two small chondroitin sulfate/dermatan sulfate proteoglycans—decorin and biglycan—and a keratan sulfate proteoglycan—fibromodulin—display considerable homology, demonstrated by the presence of several 24–amino-acid leucine-rich repeats [4–6]. These repeats are thought to mediate interactions of these proteoglycans with other matrix molecules, as demonstrated by the ability of decorin to bind to types I, II, and VI collagen fibrils and to fibronectin [1–3]. In adult human skin, decorin is abundant throughout the dermal layer, especially in the papillary dermis, whereas biglycan is localized exclusively at the dermoepidermal border [7].

Formation of dermal extracellular matrix is regulated by various polypeptide growth factors [8]. The most potent stimulator of connective tissue formation is transforming growth factor-β (TGF-β), which plays an important role in wound repair and has also been implicated in the pathogenesis of dermal fibrosis [8,9]. We and others have shown previously that in fibroblasts, TGF-β markedly enhances expression of biglycan, whereas expression of decorin is potently down-regulated [10–13]. However, the effects of TGF-β on decorin expression appear to be cell specific, because in lung epithelial and kidney mesangial cells, TGF-β has been shown to enhance expression of decorin [14,15]. Interestingly, both decorin and biglycan have been shown to inhibit cellular response to TGF-β by binding it with their core proteins [16,17].

Glucocorticoids are widely used to treat a variety of inflammatory disorders because of their potent anti-inflammatory properties. One of the side effects of long-term use of both systemic and topical glucocorticoids is dermal atrophy, mainly due to reduction in the amount of collagen, the major component of dermal extracellular matrix [18]. In cell culture conditions, glucocorticoids suppress expression of types I and III collagen and elastin by dermal fibroblasts [19,20]. Retinoids are used in dermatology for treatment of hyperproliferative and keratinization disorders, as well as acne. Retinoic acid has also been shown to stimulate formation of dermal connective tissue, especially type I collagen gene expression in photodamaged skin [21–23].

In this study, we show that decorin gene expression is potently stimulated by dexamethasone and suppressed by retinoic acid. In addition, TGF-β–elicited suppression of decorin and enhancement of biglycan expression are potently inhibited by dexamethasone. These results suggest that the effects of glucocorticoids and retinoids on dermal connective tissue are partially mediated by altered expression of decorin and biglycan.

MATERIALS AND METHODS

Cell Cultures Human skin fibroblast cultures were established from punch biopsy specimens obtained from voluntary healthy donors. The cell

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cultures were maintained in Dulbecco's modification of Eagle's medium (DME) supplemented with 10% fetal bovine serum (FBS), 2 mM glutamine, 100 U/ml penicillin-G, and 100 μg/ml streptomycin. For RNA analysis, cell cultures were maintained for 18 h in DME supplemented with 1% FBS in experiments with retinoic acid alone, or with 10% FBS in experiments with dexamethasone alone. Thereafter, dexamethasone or all-*trans*-retinoic acid (both from Sigma Chemical Co., St. Louis, MO) was added in the concentrations indicated, and the incubations were continued for 24 h. In experiments in which TGF-β was used, the cells were first incubated for 18 h in DME supplemented with 1% FBS, and 5 ng/ml TGF-β1 or 2 (kindly provided by Dr. David Olsen, Celtrix Laboratories, Santa Clara, CA) was added to the culture media 1 h after addition of dexamethasone or retinoic acid (1 μM each).

RNA Analysis Total cellular RNA was isolated from cell cultures using the guanidine thiocyanate/cesium chloride method [24]. Aliquots of total RNA (15 μg) were fractionated on 0.8% agarose gels containing 2.2 M formaldehyde, transferred to Zeta Probe filter (BioRad, Richmond, CA) by vacuum transfer (VacuGene XL; LKB, Bromma, Sweden), and immobilized by heating at 80°C for 30 min. The filters were prehybridized for 2 h and subsequently hybridized for 20 h with cDNAs labeled by [α-^{32}P]dCTP using random priming [25]. The filters were then washed; the final stringency of washes was 0.1 × standard saline citrate/0.1% sodium dodecylsulfate (SDS) at 60°C for human cDNAs and 52°C for rat glyceraldehyde-3-phosphate dehydrogenase (GAPDH) cDNA. The [^{32}P]cDNA-mRNA hybrids were visualized by autoradiography, and the levels of mRNAs were quantitated by densitometric scanning of the x-ray films using MCID software (Imaging Research Inc., St. Catharines, Ontario, Canada). The following cDNAs were used for hybridizations: a 1.8-kilobase pair (kb) human decorin cDNA [4] (kindly provided by Dr. Tom Krusius), a 1.6-kb human biglycan cDNA [5] (kindly provided by Dr. Larry Fisher), a 0.7-kb human proα1(III) collagen cDNA [26] (kindly provided by Dr. Eero Vuorio), and a 1.3-kb rat GAPDH cDNA [27] (kindly provided by Dr. P. Fort).

Proteoglycan Analysis For analysis of proteoglycan production, the cells were first incubated for 18 h in DME supplemented with either 1% FBS in experiments with retinoic acid and/or TGF-β, or with 10% FBS in experiments with dexamethasone alone. Thereafter, the cultures were preincubated with dexamethasone, retinoic acid, or TGF-β, alone or in combinations for 24 h. The incubation media were then replaced with similar media containing the same combination of effector molecules and $^{35}SO_4$ (100 μCi/ml; Amersham International, Amersham, UK), and the incubations were continued for 48 h.

Proteoglycans in media samples were precipitated by end-to-end overnight incubation with 20 μl/ml of 50% (w/v) diethylaminoethyl (DEAE) Sephacel (Pharmacia LKB, Sweden) in 20 mM Tris-HCl (pH 7.5), 0.1% (w/v) Triton X-100, and 0.15 M NaCl at 4°C. The pellets were washed twice with 1 ml of the same buffer and twice with 1 ml of the buffer containing 0.2 M NaCl. The pellets were then dissolved in SDS buffer (10 mM sodium phosphate, pH 7.0, 2% [w/v] SDS, 10% [v/v] glycerol, and 0.003% [w/v] Bromphenol Blue). The optimal amount of 50% DEAE Sephacel needed for precipitation of all precipitable radioactivity in the samples was tested by using different concentrations of 50% DEAE Sephacel (data not shown). An equal volume from each sample was boiled for 3 min and fractionated on SDS-polyacrylamide gel electrophoresis (PAGE) with 4% stacking and 7.5% resolving gels [28]. The gels were fixed, enhanced, dried, and exposed to x-ray films. Decorin and biglycan were identified based on the molecular weight as described previously [10,29,30]. The relative amounts of $^{35}SO_4$-labeled proteoglycans were quantitated by densitometry as mentioned above and corrected for cell numbers, measured as described previously [31].

RESULTS

Dexamethasone Enhances Decorin Gene Expression by Dermal Fibroblasts In the initial experiment, regulation of decorin gene expression by dexamethasone was studied at the level of proteoglycan production. Human dermal fibroblasts were treated with various concentrations of dexamethasone in DME supplemented with 10% FBS and labeled with $^{35}SO_4$. Labeled proteoglycans were precipitated with DEAE Sephacel and analyzed by SDS-PAGE, which allowed detection of decorin and biglycan based on the molecular weight [10,29,30]. As shown in **Fig 1**, dexamethasone clearly enhanced production of decorin in a dose-dependent manner. Quantitation of decorin levels indicated that the maximal enhancement (4.8-fold) was noted with a concentration of 10^{-8} M **(Table I)**. In the same cells, production of biglycan

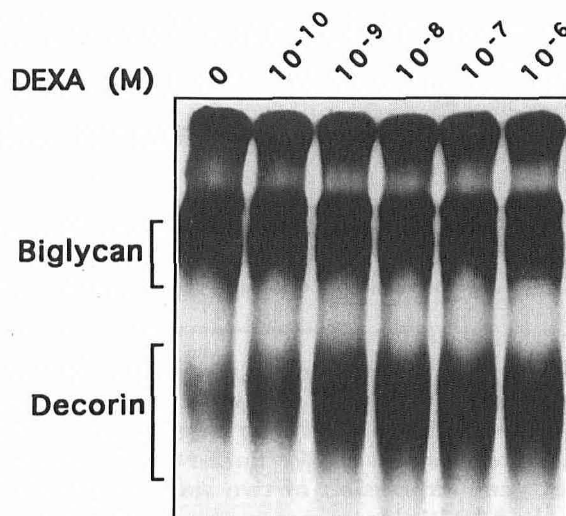

Figure 1. Dexamethasone enhances decorin production by dermal fibroblasts in culture. Confluent cultures of human skin fibroblasts were preincubated for 24 h with various concentrations of dexamethasone (DEXA), as indicated, in DME supplemented with 10% FBS. The cells were then labeled with $^{35}SO_4$ in similar media for 48 h. The labeled proteoglycans were precipitated with DEAE Sephacel, fractionated on 7.5% SDS-PAGE, and visualized by fluorography. The migration positions of biglycan and decorin are indicated.

was not altered by dexamethasone **(Fig 1; Table I)**. The relative molecular mass of decorin or biglycan molecules was not markedly altered in cultures treated with dexamethasone, indicating that under these conditions, dexamethasone did not affect the length of the single chondroitin sulfate/dermatan sulfate side chain attached to decorin core protein, or of the two chondroitin sulfate/dermatan sulfate side chains attached to biglycan core protein **(Fig 1)**. Dexamethasone treatment of dermal fibroblasts had no marked effect on cell number (not shown).

To examine whether increased production of decorin in fibroblast cultures treated with dexamethasone was due to an increase in cellular levels of decorin gene transcripts, we performed Northern analysis with RNA from cells treated with various concentrations of dexamethasone in DME containing 10% FBS. Incubation of dermal fibroblasts with dexamethasone clearly increased decorin mRNA abundance in a dose-dependent manner **(Fig 2)**. GAPDH mRNA

Table I. Dose-Dependent Enhancement of Decorin Production and mRNA Levels by Dexamethasone[a]

	Dexamethasone Concentration (M)					
	0	10^{-10}	10^{-9}	10^{-8}	10^{-7}	10^{-6}
Proteoglycan production						
Decorin	4.91	8.21	18.35	23.80	18.42	14.69
	(1.00)	(1.67)	(3.74)	(4.84)	(3.75)	(2.99)
Biglycan	52.79	62.33	60.43	55.14	52.68	48.81
	(1.00)	(1.18)	(1.14)	(1.04)	(1.00)	(0.92)
mRNA levels						
Decorin	4.68	ND	7.31	10.08	10.90	9.93
	(1.00)		(1.56)	(2.15)	(2.33)	(2.12)
Biglycan	7.90	ND	7.20	7.46	7.86	6.52
	(1.00)		(0.91)	(0.94)	(0.99)	(0.83)

[a] Proteoglycan production was assayed as indicated in the legend for **Fig 1**. Levels of decorin and biglycan were quantitated by densitometric scanning of x-ray films. The values represent densitometric units corrected for cell numbers. Biglycan and decorin mRNA abundance was assayed as indicated in the legend for **Fig 2** and quantitated by densitometric scanning of x-ray films. The values represent densitometric units corrected for GAPDH mRNA levels in the same samples. The values in parentheses indicate values relative to the levels in untreated control samples (1.00). ND, not determined.

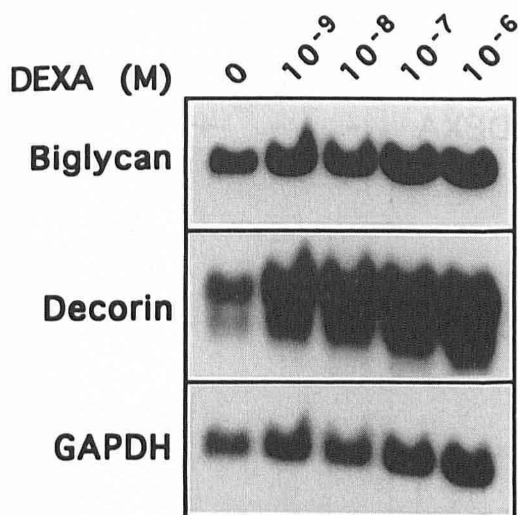

Figure 2. Dexamethasone enhances decorin mRNA levels in dermal fibroblasts. Confluent human skin fibroblasts were incubated for 24 h with various concentrations of dexamethasone (DEXA), as indicated, in DME supplemented with 10% FBS. Aliquots of total cellular RNA (15 μg) were analyzed by Northern blot hybridizations with cDNA probes for decorin, biglycan, and GAPDH as indicated.

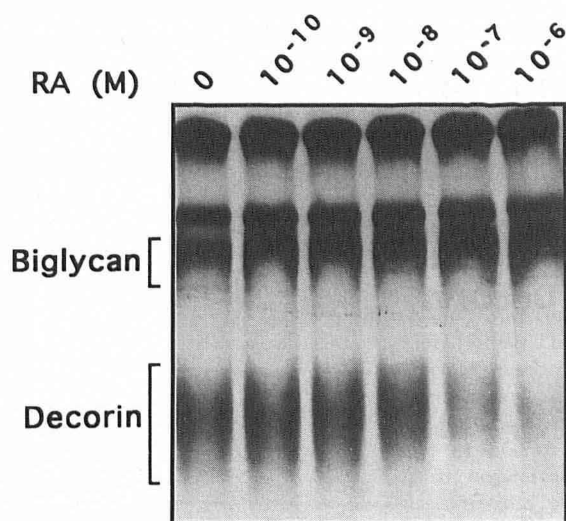

Figure 3. Retinoic acid suppresses decorin production by dermal fibroblasts. Confluent cultures of human skin fibroblasts were preincubated for 24 h with various concentrations of retinoic acid (RA), as indicated, in DME containing 1% FBS. Thereafter, the cells were labeled with $^{35}SO_4$ in similar media for 48 h. The labeled proteoglycans were precipitated with DEAE Sephacel, fractionated on 7.5% SDS-PAGE, and visualized by fluorography. The migration positions of biglycan and decorin are indicated.

levels appeared somewhat increased in cultures treated with dexamethasone, reflecting differences in the loading of total RNA. Quantitation of decorin mRNA levels and correction for GAPDH mRNA abundance in the same samples revealed maximal enhancement (2.3-fold) with a dexamethasone concentration of 10^{-7} M **(Table I)**. On the other hand, levels of biglycan mRNA were not markedly altered as compared with GAPDH mRNA levels in the same samples **(Fig 2, Table I)**.

Retinoic Acid Suppresses Decorin Gene Expression by Dermal Fibroblasts Human skin fibroblasts were also treated with various concentrations of retinoic acid (ranging from 10^{-10} to 10^{-6} M) in DME supplemented with 1% FBS and labeled with $^{35}SO_4$ for a period of 48 h. Analysis of labeled proteoglycans in the media revealed that retinoic acid treatment resulted in a dose-dependent reduction in decorin production **(Fig 3)**. Quantitation of decorin production showed a maximal reduction down to 28% of the levels in untreated control cultures, using a concentration 10^{-6} M **(Table II)**. In the same media samples, production of biglycan was not markedly altered by retinoic acid **(Fig 3, Table II)**. Treatment of skin fibroblasts with retinoic acid did not markedly alter cell number (not shown).

We also examined the effect of retinoic acid on decorin and biglycan mRNA levels in dermal fibroblasts using Northern blot hybridizations. The results show that the abundance of decorin gene transcripts was reduced in a dose-dependent manner by retinoic acid treatment of the cells **(Fig 4)**. Quantitation of decorin mRNA abundance indicated a maximal reduction, down to 49% of the levels in untreated control cells, with a retinoic acid concentration of 10^{-6} M **(Table II)**. Biglycan mRNA levels were not markedly altered by retinoic acid at any of the concentrations used **(Fig 4, Table II)**.

Dexamethasone Abrogates TGF-β–Elicited Suppression of Decorin Gene Expression by Dermal Fibroblasts Previously, TGF-β has been shown to suppress decorin gene expression at a pretranslational level by human dermal and gingival fibroblasts [10]. In this study, we also examined whether dexamethasone or retinoic acid affects TGF-β–elicited down-regulation of decorin gene expression. Analysis of $^{35}SO_4$-labeled proteoglycans by SDS-PAGE indicated that TGF-β (5 ng/ml) potently reduced secretion of decorin into culture media, down to 36% of the levels in control cells, and that dexamethasone (1 μM) inhibited the suppression of decorin production by TGF-β **(Fig 5*A,B*)**. On the other hand, retinoic acid had no effect on TGF-β–elicited down-regulation of decorin production **(Fig 5*A,B*)**.

To examine whether the inhibition of TGF-β–elicited reduction in decorin synthesis by dexamethasone reflects alterations in decorin mRNA levels, Northern blot analysis was also performed. Treatment of cells with TGF-β (5 ng/ml) resulted in a marked reduction (down to 46%) in decorin mRNA levels **(Fig 6)**. Exposure of the cells simultaneously to dexamethasone (1 μM) and TGF-β prevented the suppression of decorin mRNA levels by TGF-β **(Fig 6)**. In contrast, retinoic acid had no effect on the TGF-β–elicited reduction in decorin mRNA levels **(Fig 6)**.

Dexamethasone Inhibits Enhancement of Biglycan Gene Expression by Dermal Fibroblasts Because dexamethasone potently prevented the effect of TGF-β on decorin gene expression,

Table II. Dose-Dependent Suppression of Decorin Production and mRNA Levels by Retinoic Acid[a]

	Retinoic Acid Concentration (M)					
	0	10^{-10}	10^{-9}	10^{-8}	10^{-7}	10^{-6}
Proteoglycan production						
Decorin	51.70	51.87	41.49	45.43	19.98	14.70
	(1.00)	(1.00)	(0.80)	(0.88)	(0.39)	(0.28)
Biglycan	32.24	29.78	26.22	37.21	43.57	41.61
	(1.00)	(0.92)	(0.81)	(1.15)	(1.35)	(1.29)
mRNA levels						
Decorin	18.55	21.09	14.41	15.86	12.05	9.10
	(1.00)	(1.14)	(0.78)	(0.85)	(0.65)	(0.49)
Biglycan	7.05	10.24	8.04	9.21	5.12	5.94
	(1.00)	(1.45)	(1.14)	(1.31)	(0.73)	(0.84)

[a] Proteoglycan production was assayed as indicated in the legend for **Fig 2**. Levels of decorin and biglycan were quantitated by densitometric scanning of x-ray films. The values represent densitometric units corrected for cell numbers. Biglycan and decorin mRNA abundance was assayed as indicated in the legend for **Fig 4** and quantitated by densitometric scanning of x-ray films. The values represent densitometric units corrected for GAPDH mRNA levels in the same samples. The values in parentheses indicate values relative to the levels in untreated control samples (1.00).

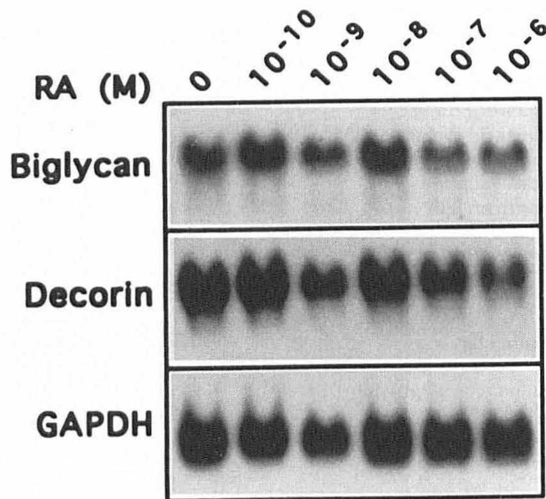

Figure 4. Retinoic acid reduces decorin mRNA abundance in dermal fibroblasts. Confluent human skin fibroblasts were incubated for 24 h with various concentrations of retinoic acid (RA), as indicated, in DME supplemented with 1% FBS. Aliquots of total cellular RNA (15 μg) were analyzed by Northern blot hybridizations with cDNA probes for decorin, biglycan, and GAPDH as indicated.

it was also of interest to examine whether dexamethasone can alter the enhancement of biglycan production and mRNA levels by TGF-β in human dermal fibroblasts. Analysis of $^{35}SO_4$-labeled proteoglycans with SDS-PAGE revealed a marked (3.8-fold) stimulation of biglycan production by TGF-β (5 ng/ml) **(Fig 5*A,B*)**. Interestingly, dexamethasone (1 μM) partially prevented the TGF-β–elicited enhancement of biglycan production, whereas retinoic acid had no significant effect on the up-regulation of biglycan synthesis by TGF-β **(Fig 5*A,B*)**.

In accordance with the findings above, treatment of cells with TGF-β (5 ng/ml) enhanced biglycan mRNA levels (2.3-fold), and simultaneous treatment of cells with dexamethasone (1 μM) and TGF-β reduced biglycan mRNA levels to the levels in control cells **(Fig 7)**. Dexamethasone alone did not affect biglycan mRNA levels as compared with GAPDH mRNA levels. In addition, dexamethasone abolished the up-regulation (2.0-fold) of type III collagen mRNA levels by TGF-β in the same cells **(Fig 7)**. In contrast to biglycan mRNA levels, dexamethasone alone reduced type III collagen mRNA abundance down to 40% of the levels in control cells, after correction for GAPDH mRNA levels in the same samples **(Fig 7)**.

DISCUSSION

Proteoglycans are components of extracellular matrix that interact with other matrix components *via* both their core proteins and glycosaminoglycan side chains [1,2]. In addition, extracellular matrix proteoglycans can regulate cellular growth-factor responses by interacting with polypeptide growth factors, again with either their core protein or glycosaminoglycan side chains [3,32]. Specifically, the extracellular matrix chondroitin sulfate/dermatan sulfate proteoglycans decorin and biglycan have been shown to bind TGF-β *via* their core proteins, thus preventing binding of TGF-β to its cell-surface receptors [16,17].

In this study, we describe the effects of two therapeutically used modified hormones, dexamethasone and retinoic acid, alone and in combination with TGF-β, on decorin and biglycan expression by dermal fibroblasts. The results indicate that dexamethasone enhances decorin gene expression at the pretranslational level and inhibits TGF-β–elicited suppression of decorin gene expression as well as up-regulation of biglycan gene expression in human dermal fibroblasts. Retinoic acid, in turn, potently inhibits decorin gene expression, but has no effect on expression of biglycan or on the effect of TGF-β on biglycan and decorin gene expression.

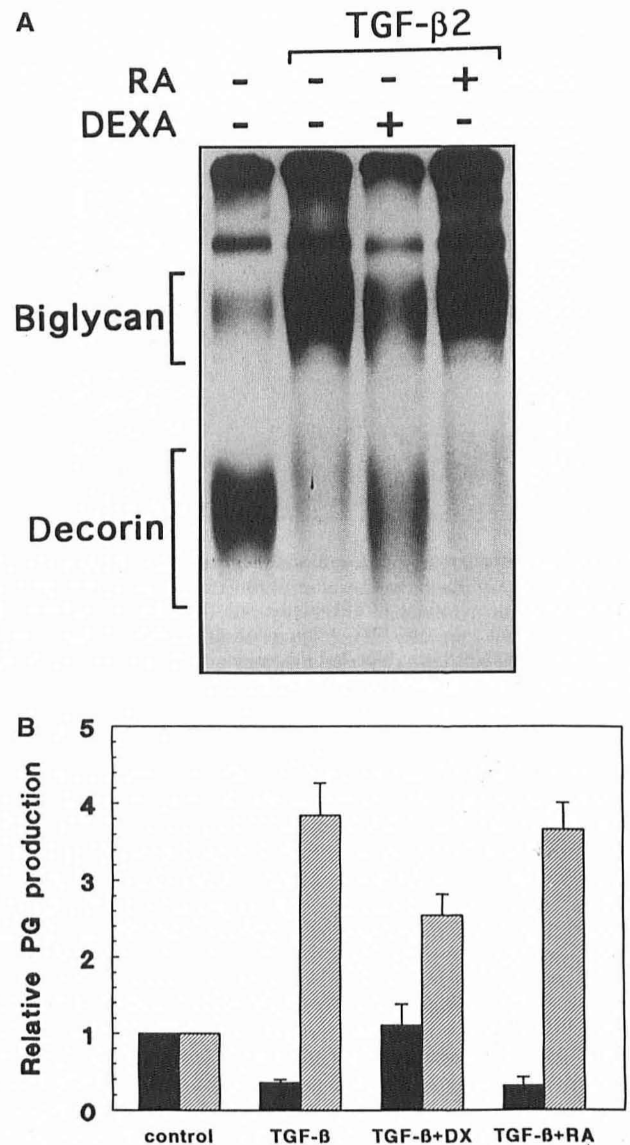

Figure 5. Dexamethasone prevents TGF-β–elicited down-regulation of decorin production and enhancement of biglycan production by dermal fibroblasts. *A*) Confluent cultures of human skin fibroblasts were preincubated for 24 h with TGF-β2 (5 ng/ml) alone or in combination with dexamethasone (DEXA) or retinoic acid (RA) (both 1 μM), as indicated, in DME containing 1% FBS. The cells were then labeled with $^{35}SO_4$ in similar media for 48 h. The labeled proteoglycans were precipitated with DEAE Sephacel, fractionated on SDS-PAGE, and visualized by fluorography. The migration positions of biglycan and decorin are indicated. *B*) Decorin (*solid bars*) and biglycan (*shaded bars*) proteoglycan (PG) production was quantitated by scanning densitometry of x-ray films. The data represent mean ± SEM from three independent experiments. The decorin and biglycan production rates for each experiment were corrected for cell number and calculated relative to the levels in untreated control samples (1.00). DX, dexamethasone.

Glucocorticoids potently suppress expression of types I and III collagens, as well as elastin, by dermal fibroblasts at the posttranscriptional level [18–20]. It is possible that the enhancing effect of dexamethasone on decorin gene expression takes place at the transcriptional level. The available nucleotide sequence of the 5′-flanking region of the human decorin gene does not contain glucocorticoid-responsive elements required for activation of transcription by glucocorticoids [33]. Such elements may, however, reside outside the regulatory sequences currently available. Re-

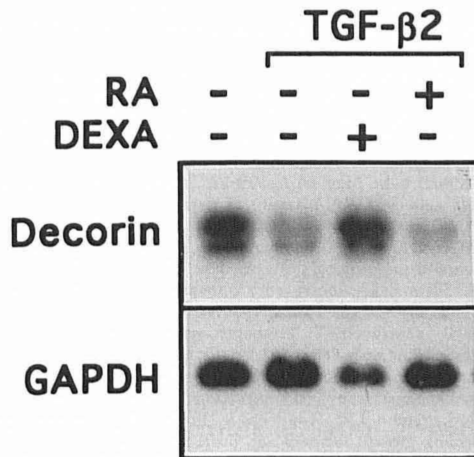

Figure 6. Dexamethasone inhibits TGF-β–elicited down-regulation of decorin mRNA levels. Confluent human skin fibroblasts were incubated for 24 h with TGF-β2 (5 ng/ml) alone or in combination with dexamethasone (DEXA) (1 μM) or retinoic acid (RA) (1 μM), as indicated, in DME supplemented with 1% FBS. Thereafter, aliquots (15 μg) of total cellular RNA were analyzed by Northern blot hybridizations using cDNA probes for decorin and GAPDH.

gardless of the activation mechanism, it is conceivable that stimulation of decorin production by glucocorticoids may result in inhibition of the cellular TGF-β response, which further potentiates the inhibitory effects of glucocorticoids on the expression of connective tissue genes, such as those for types I and III collagen and elastin, which are susceptible to activation by TGF-β [8].

The role of excessive accumulation of decorin in the pathogenesis of glomerulosclerosis in experimentally induced glomerulonephritis in rats has been unequivocally demonstrated [34]. Activation of decorin gene expression in this fibrosis model appears to be mediated by TGF-β, because neutralizing antibodies against TGF-β can prevent accumulation of decorin and subsequent glomerulosclerosis [35]. In another model of tissue fibrosis, bleomycin-induced pulmonary fibrosis in rats, enhanced expression of biglycan gene has been documented, whereas expression of decorin was not altered [36]. In addition, in fibroblasts cultured from the lesional skin of patients with systemic or localized scleroderma, expression of decorin mRNA was not increased in cells expressing elevated levels of type I collagen mRNA, indicating that decorin gene expression is not enhanced in dermal fibrosis [37]. The expression of biglycan in dermal fibrosis has not been examined, but it is likely that enhanced deposition of biglycan may also contribute to the formation of fibrotic dermal extracellular matrix in disorders such as scleroderma and keloids.

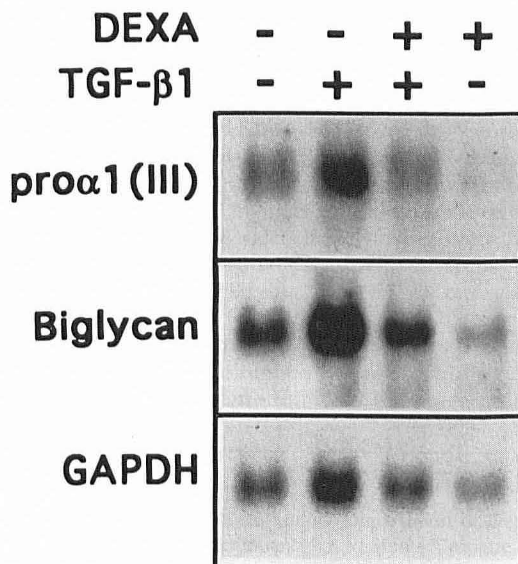

Figure 7. Dexamethasone prevents enhancement of biglycan mRNA levels by TGF-β in dermal fibroblasts. Confluent human skin fibroblasts were incubated for 24 h with TGF-β1 (5 ng/ml) or with dexamethasone (DEXA) (1 μM) alone or in combination, as indicated, in DME supplemented with 1% FBS. Aliquots (15 μg) of total cellular RNA were analyzed by Northern blot hybridizations with cDNA probes for proα1(III) collagen, biglycan, and GAPDH.

Glucocorticoids have been shown to inhibit the formation of new connective tissue in a rat wound-healing model [38,39]. The results of this study suggest that the antifibrotic effect of glucocorticoids may also be indirectly mediated by increased production of decorin, which in turn may inhibit binding of TGF-β to fibroblasts. This effect may be potentiated further by inhibition of TGF-β–elicited suppression of decorin expression. It is also conceivable that increased production of decorin by fibroblasts treated with glucocorticoids results in the formation of looser collagenous matrix because of inhibition of type I collagen fibril formation by decorin [1,2].

Retinoic acid has been shown to stimulate the formation of dermal extracellular matrix, especially deposition of type I collagen in the upper dermal layer of photodamaged skin [21–23]. This may be due to retinoic-acid–elicited enhancement of expression of TGF-β1 and 2 by epidermal keratinocytes [23,40]. The results of the present study suggest that the enhancing effect of retinoic acid on dermal connective tissue may also be potentiated *via* reduced production of decorin, which results in increased availability of TGF-β in the dermal extracellular milieu. These results are in accordance with earlier observations indicating reduction of decorin mRNA levels in dermal fibroblasts by 13-*cis*-retinoic acid [41].

In conclusion, the results of this study indicate that decorin expression and biglycan expression are effectively but differentially regulated by glucocorticoids and retinoids. These observations suggest that the effects of glucocorticoids and retinoids on dermal connective tissue may also be partially mediated *via* altered deposition of extracellular matrix proteoglycans, especially decorin. These findings also provide prospects for development of novel therapeutic strategies for disorders characterized by tissue fibrosis.

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