Deficient Expression of the Gene Coding for Decorin in a Lethal Form of Marfan Syndrome*

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Marfan syndrome is an autosomal dominant connective tissue disorder with varying abnormalities of the eye, aorta and skeleton (1, 2). The genetic defect behind this disorder is not known. Biochemical studies have shown defects in cross-links of collagen and elastin fibers (3–6). The only finding at the protein level so far has been reported already in 1981 (7) leading to Marfan syndrome in the studied families (10–14).

Here we have used a different approach and studied the mRNA levels of different connective tissue components in the skin fibroblasts of several Marfan patients. Of particular interest was a Swedish family in which both parents had the disease. In the fibroblasts of their lethally sick offspring we found the decreased level of transcription and translation of decorin, (DSPGII), a dermatan/chondroitin sulfate proteoglycan, which is the major sulfated product of fibroblasts and smooth muscle cells (16, 17). Transcription of decorin was also decreased in 3 out of 12 other unrelated Marfan patients studied.

Proteoglycans are abundant components of the connective tissue matrix. They exist in many different forms, some of which are tissue- or cell type-specific. The functional roles of proteoglycans are only partially understood (15). Our finding, the deficient transcription of decorin in several Marfan patients, gives new insights to the significance of different matrix components in the formation of biologically functional connective tissue.

MATERIALS AND METHODS

Marfan Family—The pedigree of the studied Swedish Marfan family is given in Fig. 1. The clinical findings have been described in detail by Schollin et al. (18). In short, the affected newborn boy was the second child and was born at term after a normal pregnancy. He had symptoms from the skin with multiple skinfolds at birth and from mitral and aortic insufficiency. He suffered from many upper respiratory tract infections during the first months and died at 5 months of age of a pneumonia. Postmortem findings confirmed the cardiac malformations found earlier at echocardiography. Both the father and mother demonstrated several symptoms of Marfan syndrome and fulfilled the diagnostic criteria for this disease (18).

Reagents—Random prime DNA labeling kit was purchased by BRL (Bethesda Research Laboratories Life Technologies Inc.). Fall Biozym, nylon membranes used in Northern blots were prepared by Fall Ultrafine Filtration Corporation (Glen Cove, NY). [35S]Deoxy-xytidine triphosphate, [35S]methionine, [35S]sulfate, [125I]protein A, and [14C]-methylated protein marker mixture were obtained from Amersham, United Kingdom. Dulbecco's modified Eagle's medium (DMEM), RPMI 1640 medium, and fetal calf serum (FCS) were purchased from Gibco, UK. Growth factors IL-1β and TGF-β1 were purified by R & D systems (R & D systems, Inc., Minneapolis, MN).

Fibroblast Cultures and Labeling Conditions—Fibroblast cultures were established from skin biopsies from the proband and his parents. The control cultures included fibroblasts from the skin biopsies of...
Marfan syndrome; t, proband. The family is described in detail by Schollin et al. (18), Marfan syndrome: a lethal form of the syndrome in an infant who may have inherited a Marfan gene from both of his parents. The mRNA levels of different connective tissue components including type I, III, and VI collagens, versican (fibroblast chondroitin sulfate proteoglycan), and decorin were studied in the cultured skin fibroblasts of the affected offspring and his parents.

The mRNA levels of type I and the α1 and α2 chains of type VI collagen genes in the fibroblasts of the infant did not differ significantly from those of his parents' and control fibroblasts (Fig. 2). The mRNA level of α3(VI) collagen in the infants fibroblasts was higher than his parents but did not differ from the levels of the several age-matched controls, which demonstrated a significant variation, e.g. the signals from fetal and infant fibroblasts compared to adult fibroblasts were considerably higher. Type III collagen mRNA level was slightly decreased both in the fibroblasts of the offspring and his mother (Fig. 2). However, the most significant finding was the markedly decreased mRNA level of decorin in the fibroblasts of the offspring. On the basis of scanning of the hybridization signals of slot dot filters it was only 10% from the level of age-matched controls (Fig. 3). Contrary to our expectations the cultured fibroblasts of the parents of the offspring did not demonstrate clearly decreased levels of decorin mRNA. The mRNA levels of the father and mother were 80 and 135% of adult controls, respectively. It should be noted that the control cells used in this study included skin fibroblasts from 11- and 30-month-old infants as well as from skin biopsies of adult individuals (34 and 42 years of age). All of the samples were taken in accordance with Helsinki declaration. Cells from passages 3-9 were cultured in DMEM containing 10% inactivated FCS, 50 units/ml penicillin, 50 μg/ml streptomycin, and 50 μg/ml ascorbate. Fibroblast cultures were incubated 24 h in fresh medium before collecting them for RNA extraction.

For growth factor experiments, the fibroblasts were preincubated in the medium containing 2% dialyzed FCS for 24 h following the incubation in the same medium with addition of IL-1 (5 units/ml) (19) and TGF-β1 (250 pm) (20) for 24 h before collecting the RNAs. For protein studies the cells were cultured to about 75% confluence in DMEM containing 10% inactivated FCS, 50 units/ml penicillin, 50 μg/ml streptomycin, and 50 μg/ml ascorbate. Fibroblast cultures were incubated 24 h in fresh medium before collecting them for RNA extraction.

RESULTS

Transcription of Decorin and Other Connective Tissue Components— The family studied here represents a rare type of Marfan syndrome: a lethal form of the syndrome in an infant who may have inherited a Marfan gene from both of his parents. The mRNA levels of different connective tissue components including type I, III, and VI collagens, versican (fibroblast chondroitin sulfate proteoglycan), and decorin were studied in the cultured skin fibroblasts of the affected offspring and his parents.

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RNA Isolation and Northern Analysis—Total RNA from confluent cell layers was isolated by the guanidium isothiocyanate method described by Chirgwin et al. (26). For Northern analysis 15 μg of total RNA was electrophoresed in formaldehyde-agarose gel and transferred onto a Pall Biodyne™ nylon membrane. The specific inserts of the following clones were radioactively labeled to a specific activity of 5×10^8 dpm/μg with [32P]dCTP using the primer extension reaction: α1(I) collagen (a 2.6-kb BamHI genomic fragment (27)), α2(I) collagen (2.2-kb cDNA (28)), α1(III) collagen (a 600-base pair PstI/HindIII fragment of the 3’ end of the cDNA (29)), α1(VI), α2(VI), and α3(VI) collagen (2.0-, 1.5-, and 1.6-kb cDNA clones (30)), versican (a 700-base pair EcoRI fragment of the cDNA clone (23, 31), and decorin (1.8-kb full length cDNA clone (22). Prehybridization (1-4 h) and hybridization (18 h) of the filters were performed in 5× SSC (0.75 M NaCl, 0.075 M Na citrate buffer, pH 7.0), 50% formamide, 0.05 M phosphate buffer, pH 6.5, 5× Denhardt’s (1% (w/v) Ficoll, 1% (w/v) polyvinylpyrrolidone, 1% (w/v) bovine serum albumin), 250 μg/ml herring DNA, 0.1% SDS at 42 °C. After washing in 2× SSC, 0.1% SDS the filters were exposed on Kodak X-Omat films with intensifying screens for 1-7 days at -80 °C.

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FIG. 2. Analyses of the mRNA levels of several connective tissue components in the cultured fibroblasts of a Swedish Marfan family. Total RNA was isolated from the cultured fibroblasts of two controls (C1 and C2), the offspring (O), and the mother (M) and the father (F) of the offspring. Identical filters in which there was 15 μg of RNA/lane were hybridized with the probes specific for the genes coding for α1(I), α2(I), α1(III), α1(VI), α2(VI), and α3(VI) collagen genes. To ascertain the identical quantity of RNA applied to each well, an aliquot of the same sample was used to determine the concentration just before applying it to the gel. Furthermore, the filters were constantly also hybridized with the probe for γ-actin to confirm the quantity still on the filter (47).

FIG. 3. The analysis on the mRNA levels of decorin and versican in the cultured fibroblasts of the Swedish Marfan family. The RNA filter identical to the one in Fig. 2 and a slot dot RNA filter with different quantities of total RNA were hybridized with the decorin (DSPGII) cDNA probe. The two transcripts of decorin (DSPGII) are indicated with arrows. The same RNA filter was hybridized also with the versican (CSPG) cDNA.

The relative proportions of the proteoglycans produced by the fibroblasts varied. Control fibroblasts produced mainly decorin, whereas fibroblasts from the Marfan patients synthesized both proteoglycans (Fig. 4). In the case of the offspring biglycan was the major product.

Decorin produced by fibroblasts of the offspring was studied by Western blotting and immunoprecipitation. Fig. 5 shows the results obtained by Western blotting of chondroitinase ABC-treated samples. In accordance with the reduced level of chondroitin or dermatan sulfate proteoglycans. The results suggest that the proteoglycans correspond to DSPGI (biglycan) and DSPGII (decorin) (32). These are the major secreted proteoglycans of fibroblast cultures (17) and are coded by two different genes. Some [35S]sulfate-labeled material remained in the stacking gel or at the gel interface, as is typical of large proteoglycans.

Protein Studies on Decorin—Proteoglycans were isolated by anion exchange chromatography from culture media of [35S]sulfate-labeled fibroblasts. The amount of [35S]sulfate incorporated into the proteoglycan fraction by the fibroblasts of the mother, father, and offspring were 121, 86, and 114% of that of the control fibroblasts, respectively. SDS-PAGE analysis of the proteoglycans demonstrated one or two species in the separating gel with apparent molecular masses of about 200–350 and 100–140 kDa (Fig. 4). Both proteoglycans were digested by chondroitinase ABC, as would be expected for biglycan or dermatan sulfate proteoglycans. The results suggest that the proteoglycans correspond to DSPGI (biglycan) and DSPGII (decorin) (32). These are the major secreted proteoglycans of fibroblast cultures (17) and are coded by two different genes. Some [35S]sulfate-labeled material remained in the stacking gel or at the gel interface, as is typical of large proteoglycans.
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FIG. 5. Western blot analysis of decorin from the medium of cultured fibroblasts. Culture medium from control fibroblasts (lanes 2 and 4) and from fibroblasts of the offspring (lanes 3 and 5) was digested with chondroitinase ABC and subjected to Western blot analysis. A sample corresponding to 30 µl of original medium was applied into lanes 2 and 3 and 60 µl into lanes 4 and 5. Lane 1 shows an immunoblot of decorin isolated from bovine skin.

FIG. 6. A, immunoprecipitation of decorin from the medium of cultured fibroblasts. Fibroblast cultures were labeled with [35S]methionine and media from control fibroblasts (lanes 2 and 4) and from fibroblasts of the offspring (lanes 3 and 5) were subjected to immunoprecipitation using antibodies to decorin (lanes 2 and 3) and, as a control, antibodies to versican (lanes 4 and 5). Lane 1 shows the migration of 11C-labeled Mr marker proteins. B, for the quantitation of immunoprecipitated decorin the x-ray film was scanned using a Helena Laboratories recorder. The protein band with a slightly larger apparent molecular weight than decorin core protein which coprecipitated with decorin has been subtracted from the recordings. CO, control; MA, offspring.

Decorin mRNA the fibroblasts of the offspring synthesized markedly less decorin core protein than age-matched control fibroblasts. In both cases chondroitinase ABC produced a tight doublet band which is due to differential glycosylation of the core protein by two or three N-glycosidically linked carbohydrate chains (33). The mobilities of the doublet bands obtained from the offspring and control were identical suggesting no major difference in the molecular weights of the polypeptide chains.

FIG. 7. The mRNA level of decorin in the control fibroblasts (CO) and the fibroblasts of the offspring (MA) after a 24-h incubation in the presence of TGF-β1 and IL-1β.

FIG. 8. Comparisons of the effect of TGF-β1 and IL-1β on the mRNA levels of α1(I) collagen and decorin (DSPGII) in the fibroblasts of the Marfan offspring.

FIG. 9. The mRNA levels of decorin (DSPGII) in the fibroblasts of a 1-year-old infant control (lane 1), two adult controls (lanes 2 and 3), and five Marfan patients (lanes 4–8). To control the quantity of RNA, the same RNA filter was also hybridized with the cDNA probe specific for γ-actin (47).

The amount of the synthesized core protein was quantitated by scanning of x-ray films obtained after immunoprecipitation of [35S]methionine-labeled proteoglycans or Western blotting using 125I-labeled protein A instead of alkaline phosphatase-conjugated secondary antibodies. Both methods produced equal results. The amount of decorin synthesized by the fibroblasts of the offspring accounted to only 20% of that of age-matched control fibroblasts (Fig. 6).
The Effect of TGF-β and IL-1β on the Transcription of Decorin—Two growth factors regulating the expression of matrix components, TGF-β1 and IL-1β, were used to stimulate the transcription of the decorin gene in the Marfan fibroblasts. TGF-β1 decreased the decorin transcripts about 50% in both Marfan and control fibroblast cultures, whereas IL-1β stimulated transcription, increasing the decorin specific mRNA level in control cultures two to three times but failed to have any effect on the decorin mRNA level in the fibroblasts of the affected infant (Fig. 7). The failure of decorin mRNA of the Marfan patient to respond to IL-1β was specific for the decorin gene since both TGF-β1 and IL-1β increased the mRNA level of α1(I) (Fig. 8) and α1(III) collagen genes as well as versican (data not shown) equally in the fibroblasts of both the Marfan infant and controls.

Transcription of Decorin in Other Marfan Fibroblasts—When identical mRNA analyses of connective tissue components were carried out in the cultured fibroblasts of 12 Finnish Marfan patients, the mRNA levels of type I and type III collagen genes were normal. However, in the case of three Marfan individuals, the finding similar to that described here in the lethal Marfan syndrome was established: the level of decorin mRNA was markedly decreased (see Fig. 9 for two of the patients). These three Marfan patients had demonstrated a typical clinical picture of this syndrome. Their ages are 5, 7, and 18 years and no distinct phenotypic features different from other studied Marfan individuals could be recognized. In all three cases the patients with deficient decorin transcription had inherited the Marfan syndrome from only one of the parents.

DISCUSSION

The importance of proteoglycans as structural components in connective tissue has remained to high extent unclear so far. Although decorin is an abundant component of connective tissue, its precise function is not known. It is known to bind to type I and type II collagen (34–36) and to affect the rate of collagen fibril formation (34–36). It inhibits binding of mesenchymal cells to collagen and fibronectin (37) and also inhibits cell proliferation (38). No inherited disease has so far been linked to a proteoglycan defect in humans and the only proteoglycan deficiency in animals has so far been described in chickens (39).

Our results give new insights except to the role of proteoglycans in connective tissue matrix also to the connective tissue changes that are found in the Marfan syndrome. The markedly decreased transcription of decorin gene described here in a lethal form of Marfan syndrome and also found in three other Marfan patients may lead to the disturbed arrangement of structural components in connective tissue. We confirmed that the deficient expression of decorin is not explained by the patient’s young age or by differences in the confluence or passage number (3 to 9) of the fibroblasts. Recently Vogel and Clark (17) have also reported that the expression of decorin and biglycan in fibroblast cultures is not influenced by cell confluence or donor age.

Several biochemical studies have shown defects in cross-link formation of collagen fibers in Marfan patients (3–5). Because decorin is associated with collagen fibrils and is believed to regulate collagen fibrillogenesis, it could be possible that the relative decorin deficiency in extracellular matrix would disturb cross-link formation of collagen fibers, this resulting in the decreased tensile strength of these structures. At the tissue level this could result in the cardiovascular, ocular, and skeletal manifestations typical for the Marfan syndrome.

IL-1β is reported to enhance the transcription levels of the genes coding for type I and III collagens and decorin in human skin fibroblasts (19, 40). However, this growth factor failed to stimulate the transcription of decorin in cultured fibroblasts of the Marfan infant described here. The defect leading to the lack of this response can be either in the regulatory region of decorin gene or in some other gene taking part in the regulation of the expression of decorin.

The response of the cultured fibroblasts of the Marfan patient to IL-1β was normal in the case of both type I and type III collagen as well as another proteoglycan, versican. This confirms that the low level of decorin transcription is not just a reflection of a general down-regulation of matrix components but must carry certain specificity to this proteoglycan gene.

TGF-β enhances the expression of several extracellular matrix proteins like type I collagen, fibronectin, thrombospondin, and proteoglycans (20, 41, 42). In the case of α1(I) collagen it probably stimulates the rate of transcription and it also changes the mRNA stability in confluent monolayers (42). Its effect on proteoglycans is mainly based on the stimulation of the rate of biosynthesis and depressing the rate of catabolism by decreasing the activity of different proteinases in connective tissue (20, 43–45). In our studies TGF-β decreased the mRNA levels of decorin in both control and Marfan cells. It seems that the mechanism of TGF-β as a regulator of the decorin gene expression is not mediated via the regulation of the transcription event.

Another, quantitatively smaller but constant defect found in the studied Marfan individuals was the decreased mRNA level of type III collagen in the fibroblasts of the offspring and his mother. Type III collagen is expressed in the same tissues as type I collagen but in smaller amounts. The expression of this gene is highest in the fetal period and stays at the higher level during the first years of life (46). The cultured skin fibroblasts from fetuses or young children also express higher amounts of type III collagen than corresponding cultures of grown-up individuals. However, the fibroblast culture of this Marfan infant (5 months of age) demonstrated lower levels of type III collagen mRNA than adult control cultures.

The studied Marfan infant with the severe connective tissue changes, finally dying in the disease, represents an exceptional type of Marfan patient since the Marfan mutation is present in the genome of both of his parents. Although at this stage we cannot pinpoint the actual gene defect in this Marfan patient, the deficient transcription of decorin gene, and its unresponsiveness to IL-1β reported here might have some more general significance in Marfan syndrome. We found the same phenomenon in three other, unrelated Marfan patients with a more typical inheritance pattern of this connective tissue disease, the defective gene segregating only in paternal or maternal branch of their pedigrees.

This seemingly paradoxical finding can be explained by a spectrum of mutations most probably causing Marfan syndrome. In the case of the parents of the lethally sick infant described here, the normal mRNA level of decorin may represent the dosage compensation phenomenon found in heterozygotes. In the case of the three other Marfan patients with the reduced transcription of decorin gene, among the possibilities are different mutations of the gene(s) effecting the transcription of decorin gene. These mutations could result in similar findings at the transcription level of decorin and clinical phenotype, but in different levels of compensation by the normal allele.

4 P. Mäkinen and T. Krusius, unpublished results.
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