Interactions between the Cartilage Oligomeric Matrix Protein and Matrilins

IMPLICATIONS FOR MATRIX ASSEMBLY AND THE PATHOGENESIS OF CHONDRODYSPLASIAS*

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The cartilage oligomeric matrix protein (COMP) and matrilins are abundant non-collagenous proteins in the cartilage extracellular matrix. In the presence of calcium, COMP and matrilin-1 elute together in the gel filtration of cartilage extracts and can be co-immunoprecipitated. In a screen for ligands of matrilin-1, -3, and -4 using an ELISA-style binding assay, COMP was identified as a prominent binding partner for all three, indicating a conservation of the COMP interaction among matrilins. The interaction of COMP and matrilin-4 is saturable, and an apparent $K_d$ of 1 nM was determined. However, only the full-length COMP and the full-length matrilin-4 proteins showed a strong interaction, indicating that the oligomeric structures markedly increase the affinity. Mutations in COMP or matrilin-3 cause related forms of human chondrodysplasia, and the COMP mutation D469A, which is found in patients with pseudoachondroplasia, has been shown to cause a reduced calcium binding. Despite this, the mutation causes only a slight decrease in matrilin-4 binding. This indicates that impaired binding of COMP to matrilins does not cause the pseudoachondroplasia phenotype but rather that matrilins may be co-retained in the rough endoplasmic reticulum where COMP accumulates in the chondrocytes of patients.

Although the cartilage extracellular matrix contains only a limited number of structural proteins, many aspects of their assembly into a functional matrix remain to be described. Cartilage collagen fibrils and aggrecan, assembled into large aggregates, form the major networks that provide tensile strength and elasticity, whereas other matrix proteins are believed to mediate additional steps in the matrix assembly. Of these proteins, COMP3 (1) and the four members of the matrilin family (for review see Ref. 2) are among the most abundant and share the feature of having an oligomeric structure, allowing polyvalent interactions.

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3 The abbreviations used are: COMP, cartilage oligomeric matrix protein; TC, C-terminal COMP domain; ELISA, enzyme-linked immunosorbent assay; MALDI-TOF, matrix-assisted laser desorption/ionization-time of flight; T3, thrombospondin type 3 repeat-containing COMP domain; VWA, von Willebrand factor A.

COMP is a homopentameric member of the thrombospondin protein family (for review see Ref. 3). Its N-terminal o-helical coiled-coil oligomerization domain is followed by four epidermal growth factor-like domains, eight calcium-binding thrombospondin type 3 (T3) repeats, and a globular domain (TC) at the C terminus. COMP is predominantly found in the extracellular matrix of cartilage, tendons, and ligaments and has been shown to bind to collagens I, II, and IX (4–6). Mutations in COMP can lead to two related human diseases, pseudoachondroplasia and multiple epiphyseal dysplasia (7).

The matrilins constitute a recently discovered family of extracellular matrix proteins (2). Matrilin-2 and -4 have broad tissue distributions in both dense and loose connective tissue, whereas matrilin-1 and -3 are expressed almost exclusively in skeletal tissues. In the extracellular matrix of cultured cells, matrilins are deposited in fibillar networks. All matrilins have a similar modular composition, with von Willebrand factor A (VWA)-like and epidermal growth factor-like domains followed by a C-terminal coiled-coil domain. It is thought that matrilins play a role in mediating interactions between major components of the extracellular matrix such as collagens and proteoglycans (8), and the three forms abundant in cartilage, namely matrilin-1, -3, and -4, are indeed associated with native collagen type VI microfibrils extracted from rat chondrosarcoma tissue (9). Here the matrilins are bound to the small leucine-rich repeat proteoglycans biglycan and decorin, which, in turn, interact with the N-terminal globular domains of the collagen VI molecules. When located at the periphery of the microfibrillar complex, matrilins mediate interactions with aggrecan or collagen II. Matrilin-3 is strongly up-regulated in human osteoarthritic cartilage (10), and a missense mutation in the human matrilin-3 gene was recently found to coincide with hand osteoarthritis in a group of patients in the Icelandic population (11). As in the case of COMP, mutations in the matrilin-3 gene have been shown to cause multiple epiphyseal dysplasia (12). In the present study we have identified an interaction between COMP and members of the matrilin family that is likely to be of importance both in extracellular matrix assembly and in the pathogenesis of chondrodysplasias.

EXPERIMENTAL PROCEDURES

Gel Filtration Analysis—The extraction of matrix proteins from bovine cartilage was performed essentially as described earlier (13). In brief, fresh cartilage (~100 g, wet weight) from adult bovine shoulder joints was homogenized using a Moulinex MiniPro homogenizer at full speed in 200 ml of prechilled extraction buffer (0.15 M NaCl, 10 mM Tris-HCl, pH 7.4, and 1 mM phenylmethylsulfonyl fluoride) without EDTA. Tissue residue was collected by centrifugation at 18,000 x g at 4 °C for 20 min. This wash cycle was repeated twice, each time with 10 min of homogenization. The tissue residue was then suspended in 200 ml of the same buffer containing, in addition, 10 mM EDTA and ex-
tracted for 2 h with stirring at 4 °C. The extraction with the EDTA-containing buffer was repeated twice, and the extracts were pooled. The crude extract was cleared by filtration and concentrated 100-fold by ultrafiltration. Gel filtration was performed using a pre-packed Superose 6 column (Amersham Biosciences) equilibrated with extraction buffer. For detection of the calcium-dependent co-ellation of matrix proteins, the concentrated cartilage extract was dialyzed against extraction buffer without EDTA and, finally, against extraction buffer containing 2 mM CaCl₂, which was also used during gel filtration. Fractions of 1 ml were collected and analyzed by SDS-PAGE using 10% polyacrylamide gels. Protein bands were visualized by silver stain. Peptide mapping and identification of protein bands by MALDI-TOF mass spectrometry was performed as described previously (14).

Immunoprecipitation—A bovine cartilage extract was dialyzed extensively against distilled water containing 10 μM EDTA to capture endogenous calcium. CaCl₂ was then added at concentrations as indicated in Fig. 1C, and samples were incubated for 4 h at 4 °C with protein A-Sepharose (Amersham Biosciences) pre-treated with matrilin-1 (20). Immunoprecipitation was performed three times with PBS, and co-precipitated COMP was detected by immunoblotting using a monoclonal antibody to COMP (12-C4).

Expression and Purification of Recombinant Proteins—The recombinant expression in human embryonic kidney 293/Epstein-Barr virus–nuclear antigen cells and conventional chromatographic purification as well as the use of affinity chromatography in the purification of tagged proteins have been described previously (5, 16–19). Denaturing solvents were avoided in all steps. Tags were not removed prior to binding assays. The cDNAs encoding full-length matrilin-3 and monomeric matrilin-4 lacking the coiled-coil domain were amplified by PCR using primers that inserted an SpeI restriction site at the 5′-end and a NotI site 3′-end, respectively (matn3 forward, 5′-GTTTGGCCGCCAGCCGACC-3′ and matn3 reverse, 5′-CAATGGCCGCC-GCACGATGACTTGTCCATATATTG-3′; matn4m forward, 5′-GCCACT-AGTCCGACCTCACTGCTGAGTC-3′, and matn4m reverse, 5′-CA-ATGGCGCCGCTCTGGAAACTGTGTTT-3′). After digestion with SpeI and NotI, the amplified cDNA fragments were inserted into the expression vector pCEP-Pu-StrepII-tag (C-terminal) in-frame with the sequence of the signal peptide of BM40 (20). cDNA encoding matrilin-4 VWA1 and VWA2 was amplified by PCR using primers that inserted an SpeI restriction site at the 5′-end and a NotI site 3′-end, respectively (matn3 forward, 5′-ATGCGGCCGCCTCTGGGCAAATGCTGCCTTTG-3′ and matn3 reverse, 5′-AGTCCAGCTCCAGTCTGCAGGTCC-3′). By in-gel trypsin digestion followed by MALDI-TOF mass spectrometry fingerprint analysis (not shown) and immunoblot analysis (Fig. 1B) the 60-kDa protein was identified as matrilin-1, and the 100-kDa protein was identified as COMP by immunoblot (Fig. 1B). The COMP peak was also shifted slightly toward the void volume in the presence of calcium where it co-eluted with a band of 100-kDa apparent molecular mass (Fig. 1A). In-gel trypsin digestion followed by MALDI-TOF mass spectrometry fingerprint analysis (not shown) and immunoblot analysis (Fig. 1B) the 60-kDa protein was identified as matrilin-1, and the 100-kDa protein was identified as COMP by immunoblot (Fig. 1B). The COMP peak was also shifted slightly toward the void volume in the presence of calcium, indicating an increase in mass of the COMP-containing complex. The formation of a calcium-dependent complex between COMP and matrilin-1 was confirmed by the co-precipitation of COMP when matrilin-1 was immunoprecipitated from a cartilage extract (Fig. 1C). The interaction between COMP and matrilin-1 was already saturated by the addition of calcium at a concentration of 1 μM.

Screen for Matrilin Ligands Using an ELISA-style Binding Assay—A panel of different purified proteins and proteoglycans from the cartilage extracellular matrix was tested for interactions with matrilin-1 (23), matrilin-3 (17), matrilin-4 (16), and COMP (13), respectively, followed by swine anti-rabbit immunoglobulin horseradish peroxidase conjugates (Dako Cytomation) and tetramethylbenzidine as substrate. Absorption was measured at 450 nm after stopping the reaction with 10% sulfuric acid.

RESULTS

COMP and Matrilin-1 Co-elute in Gel Filtration Performed in the Presence of CaCl₂—To identify the components of the cartilage extracellular matrix that interact in a calcium-dependent manner, the gel filtration elution profile of a bovine cartilage extract obtained in the presence of 2 mM CaCl₂ was compared with that of an extract chromatographed in the absence of divalent cations. A comparison of fractions by reducing SDS-PAGE revealed that a band with an apparent molecular mass of 100 kDa was shifted toward the void volume in the presence of calcium where it co-eluted with a band of 100-kDa apparent molecular mass (Fig. 1A). In-gel trypsin digestion followed by MALDI-TOF mass spectrometry fingerprint analysis (not shown) and immunoblot analysis (Fig. 1B) the 60-kDa protein was identified as matrilin-1, and the 100-kDa protein was identified as COMP by immunoblot (Fig. 1B). The COMP peak was also shifted slightly toward the void volume in the presence of calcium, indicating an increase in mass of the COMP-containing complex. The formation of a calcium-dependent complex between COMP and matrilin-1 was confirmed by the co-precipitation of COMP when matrilin-1 was immunoprecipitated from a cartilage extract (Fig. 1C). The interaction between COMP and matrilin-1 was already saturated by the addition of calcium at a concentration of 1 μM.

Screen for Matrilin Ligands Using an ELISA-style Binding Assay—A panel of different purified proteins and proteoglycans from the cartilage extracellular matrix was tested for interactions with matrilin-1, -3, and -4, the three matrilins most abundant in cartilage, in an ELISA-style ligand binding assay. COMP was identified as the protein giving the highest signal (Fig. 2). The fact that all three matrilins showed significant binding to COMP indicated a conservation of the COMP interaction among matrilins.

Characterization of the Interaction between Matrilin-4 and COMP—For detailed interaction studies we decided to focus on matrilin-4, as its relatively good solubility and, therefore, comparatively high purification yields allowed more extensive experimentation. Titration of the interaction of matrilin-4 with
COMP in the ELISA-style binding assay showed saturable binding and indicated an apparent $K_D$ of 1 mM (Fig. 3).

Shorter constructs of COMP and matrilin-4 were tested in ELISA-style ligand binding assays with each of the proteins being studied both in the fluid and on the solid phase. When full-length COMP was coated and different matrilin-4 proteins were used as ligands in the fluid phase (Fig. 4, A and B), the matrilin-4 full-length protein showed the strongest binding, followed by a moderate binding of a matrilin-4 monomer lacking the coiled-coil oligomerization domain. However, the single VWA domains as well as the isolated coiled-coil domain did not bind to the immobilized COMP. In an inverted assay we coated full-length matrilin-4 and the shorter forms using both full-length wild type COMP and a mutant form (D469/H9004) as ligands in the fluid phase (Fig. 4C). The COMP D469A mutation found in chondrodysplasia patients results in a decreased binding capacity for calcium (5, 24). When matrilin-4 was coated, the D469A mutant bound to the same extent as did wild type COMP (Figs. 4C and 5C). The binding to matrilin-4 was moderately decreased by the mutation when the mutant COMP was immobilized (Fig. 5B). Taken together, the results indicate only a mild influence of the mutation on binding to matrilin-4 binding, whereas the addition of EDTA completely abolished the interaction (not shown). Significant binding to full-length matrilin-4 was seen, whereas only weak binding to both VWA domains was detected, and no binding to the matrilin-4 coiled-coil domain was found (Fig. 4, C and D).

Truncated COMP proteins were also tested for binding to matrilin-4 (Fig. 5). The ELISA plate was coated with monomeric COMP lacking the N-terminal coiled-coil oligomerization domain, a protein comprising the T3 repeats together with the TC domain and the isolated TC and the coiled-coil domain in addition to full-length pentameric forms of wild type and mutant (D469A) COMP (Fig. 5, A and B). After incubation with full-length matrilin-4 in the fluid phase, strong signals were detected for both full-length wild type and mutant COMP. A weak signal was seen with the coiled-coil domain alone, whereas the monomeric COMP and the shorter constructs showed no significant binding. The addition of EDTA abolished binding (not shown). When the plate was coated with full-length matrilin-4 in an inverted assay (Fig. 5C), full-length COMP as well as the mutant COMP bound strongly, whereas monomeric COMP, the T3+TC domain pair, and the TC domain alone showed only weak interactions.

**Fig. 1. Identification of COMP-matrilin-1 complexes in extracts of bovine articular cartilage.** A, Supersose 6 gel filtration analysis of cartilage matrix proteins after extraction with EDTA in extraction buffer containing 10 mM EDTA (left panel) and after dialysis against buffer containing 2 mM CaCl$_2$ (right panel). Protein bands identified as COMP and matrilin-1 are marked. B, Immunoblot analysis of fraction 7 from the gel filtration in the presence of calcium (panel A, right) with antibodies specific for COMP (aCOMP) and matrilin-1 (aMatn1). C, co-immunoprecipitation of COMP from cartilage extracts using a matrilin-1 antibody at different CaCl$_2$ concentrations. The immunoblot was developed with an antibody specific for COMP.

**Fig. 2. Screen for matrilin ligands using an ELISA-style ligand binding assay.** A panel of different proteins and proteoglycans from cartilage extracellular matrix was tested for interactions with matrilin-1, -3, and -4. The proteins in the panel (10 µg/ml) were coated to the plastic and incubated with full-length matrilin-1 (A), matrilin-3 (B), and matrilin-4 (C) (concentration equalling 50 nM; matrilin-1, 8.7 µg/ml; matrilin-3, 10.7 µg/ml; and matrilin-4, 11.0 µg/ml) in the presence of 1 mM CaCl$_2$ for 1 h. Binding was detected in an ELISA-style manner using specific antisera directed against the matrilins. Coll, collagen; ChAd, chondroadherin; PRELP, proline arginine-rich end leucine-rich repeat protein. Abs., absorbance.

**Fig. 3. Concentration-dependence of the COMP-matrilin-4 interaction determined in an ELISA-style ligand binding assay.** Different concentrations of full-length matrilin-4 were incubated in the presence of 1 mM CaCl$_2$ with full-length wild type COMP coated onto the plastic from a 10 µg/ml solution. Binding was detected in an ELISA-style manner using a specific antiserum directed against matrilin-4. Abs., absorbance.
In either COMP, collagen IX, or matrilin-3 have been shown to cause the related pseudoachondroplasia or multiple epiphyseal dysplasia forms of chondrodysplasia (7). In pseudoachondroplasia patients carrying mutations in COMP as well as in cell culture models of this disease, COMP is retained in the rough endoplasmatic reticulum of the chondrocytes, and collagen IX co-accumulates, presumably due to the COMP-collagen IX interaction (24, 26). It is not clear at present how the mutations in matrilin-3 result in multiple epiphyseal dysplasia. Possibly, mutations in any of these three interacting proteins, namely COMP, collagen IX, or matrilin-3, result in the retention of a similar set of molecules independent of which protein actually harbors the mutation. This may explain why changes in any of these three proteins lead to a similar clinical phenotype. Indeed, in a recent review of the etiology of chondrodysplasias, Briggs and Chapman mentioned preliminary data on a high affinity binding of matrilin-3 to COMP in this context, but, in contrast to our results, the interaction was described as being cation-independent (7). In all our experiments the binding was completely abolished by the addition of EDTA. The calcium binding to COMP is well studied, and it has been determined that the mutant protein does not show the compact shape of wild type COMP but instead a more extended conformation (27). Nevertheless, it was shown that the secondary structure of COMP is not dramatically affected and that the collagen affinity is only slightly diminished (5), indicating that the structure of the individual domains is at least partially retained and that the remaining Ca\(^{2+}\) binding sites are sufficient for ligand bind-
ing. This could explain why the D469A mutation only mildly influences the COMP-matrilin interaction in our experiments. The matrilin-4 binding was moderately reduced only in assays where the COMP was immobilized, whereas binding of wild type and mutant COMP to immobilized matrilin-4 was comparable. Thus, it is likely that mutant COMP retained in the rough endoplasmic reticulum would have the capacity to interact with matrilins and reduce their secretion.

Full-length COMP binds to full-length matrilin-4 with high affinity (Fig. 3). When either full-length COMP or monomeric COMP lacking the oligomerization domain was immobilized on ELISA plates, only the full-length, pentameric protein bound matrilin-4. In contrast, immobilized full-length matrilin-4 is able to bind the COMP monomer, although this interaction appears to be much weaker than that between the oligomers. Immobilized full-length COMP binds monomeric matrilin-4, but the amount bound is significantly decreased as compared with the oligomeric form. The preference for the oligomeric protein forms indicates a multivalent binding mechanism. This is of interest because both COMP and matrilins have been shown to be prone to degradation by proteolysis (16, 28). It could be that limited proteolysis, which in both cases occurs at sites close to the coiled-coil oligomerization domains and releases almost complete but monomeric subunits, also regulates COMP-matrilin interactions in vivo. The cooperative nature of the interaction did, however, hamper our attempts to determine the protein domains in COMP and matrilin-4 that are directly involved in binding, as the truncated proteins employed gave only weak or no binding. It is likely that residual affinity remains also in truncated, monomeric proteins and that future experiments employing more sensitive binding assays or artificially oligomerized subunits will be more informative.

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