Absence of the I-10 Protein Segment Mediates Restricted Dimerization of the Cartilage-specific Fibronectin Isoform*

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2 The abbreviations used are: FN, fibronectin; DNs, deminectins; PCR-SOEing, polymerase chain reaction-sequence overlap extension; pFN, rat plasma FN; V-region, variable region of fibronectin alternative splicing.

The cartilage-specific (V + C)− fibronectin isoform does not efficiently heterodimerize with other V-region splice variants of fibronectin. To understand better the structural elements that determine this restricted dimerization profile, a series of truncated fibronectin expression constructs with various internal deletions in the V, III-15, or I-10 segments were constructed and co-transfected into COS-7 cells with either the V+C− or the (V + C)− isoform. SDS-PAGE and immunoblot analyses of the resulting conditioned media suggest that the I-10 segment must either be present in both monomeric subunits of fibronectin or absent from both subunits for efficient dimerization to occur. Further studies suggest that the I-10 segment specifically, not simply a balanced number of type I repeats at the carboxyl terminus of each monomeric subunit, plays an important role in determining different fibronectin dimerization patterns. Neither I-11 nor I-12 could be substituted for segment I-10 without significantly reducing the formation of heterodimers. Therefore, absence of segment I-10 explains why (V + C)− fibronectin is not found in heterodimeric configurations with other native V-region splice variants in cartilage. The unique dimerization pattern of (V + C)− fibronectin does not prevent matrix formation yet is consistent with this isoform having specialized properties in situ that are important for either the structural organization and biomechanical properties of cartilage or the regulation of a chondrocytic phenotype.

Fibronectin (FN)1 is an extracellular glycoprotein that has important roles in cell adhesion and migration, cell differentiation and proliferation, cell morphology and cytoskeletal organization, tissue remodeling and wound repair, and cancer progression (1). It is expressed by cells primarily in an anti-parallel dimeric configuration, composed of two 200–250-kDa monomeric subunits that are linked together by a pair of disulfide bonds near their carboxyl termini (2–4). Dimers are assembled into a fibrillar extracellular matrix that is insoluble in the detergent deoxycholate and consists of disulfide-stabilized multimers (8–11).

Alternative splicing of FN gene transcripts results in different protein isoforms. Four sites of alternative splicing have been reported, extra domain A, extra domain B, the variable (V or IIICS) region, and a cartilage-specific (C) region composed of nucleotides that encode protein segments III-15 and I-10. In adult canine and equine articular cartilage, 50–80% of the FN transcripts have an unique splicing pattern, designated (V + C)−, that deletes both the V and C regions (12). Dimerization patterns of the (V + C)− isoform were studied under native conditions within canine articular cartilage and experimentally in COS-7, NIH-3T3, and CHO-K1 cell cultures (13). In all systems, the (V + C)− isoform exists predominantly in a homodimeric configuration. Heterodimers composed of (V + C)− and the other V-region splice variants (V+C+ or V+C−) are either not observed or detected at only low levels. The homodimeric configuration of (V + C)− FN does not reflect the laws of random assortment (14, 15). By using isoform-specific constructs, it was shown that this pattern results from a problem with heterodimer formation involving the (V + C)− isoform, rather than secretion (13).

Different patterns of alternative splicing and dimerization have been shown to influence FN solubility and matrix assembly (1, 16–18). FN dimers containing the extra domain A and extra domain B domains are incorporated more efficiently into pre-existing matrices (18). In addition, Ichihara-Tanaka et al. (19) found that the segments III-15 and I-10 through I-12 are actively involved in FN matrix assembly, and deletion of even one of the type I modules reduces the matrix assembly activities. In the current study, we test the hypothesis that the restricted dimerization pattern of (V + C)− FN is related to the absence of III-15 and/or I-10 protein segments, and we study the matrix structure of this naturally occurring isoform.

EXPERIMENTAL PROCEDURES

Determinants of Heterodimerization
cDNA Constructs—Deminectins (DNs) are amino-terminal truncations of rat FN extending from within segment III-8 to the carboxyl terminus (Fig. 1). Construction of DN1, DN2, and DN3 have been described previously, and they have been shown to model accurately the dimerization profiles of native full-length FN isoforms (13, 14, 20). A series of new DN constructs, containing various V, III-15, and I-10 segment deletions, were made by PCR-sequence overlap extension (PCR-SOEing) (21, 22). The procedure involved the generation of two PCR fragments. The first fragment extended from a 5′ PatI site in the region encoding III-12 to a targeted junction site defined by the desired construct. The 5′ end of the second fragment started from the same targeted junction site and extended to a 3′ Sall site downstream of nucleotides encoding the carboxyl terminus. Oligonucleotide primers used to generate the two PCR fragments were designed with overlaps in the targeted junction region between 18 and 24 nucleotides in length (Table I). This overlap allowed fusion of the two fragments in a third

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‡The abbreviations used are: FN, fibronectin; DNs, deminectins; PCR-SOEing, polymerase chain reaction-sequence overlap extension; pFN, rat plasma FN; V-region, variable region of fibronectin alternative splicing.
A series of DN constructs, containing various V, III-15, and I-10 segment deletions, were made by PCR-SOEing steps (DN4a and DN14b). The procedure involved the generation of two PCR fragments. The first amplicon extended from a 5′ PstI site in the region encoding III-12 to a targeted junction site defined by the desired construct. The 5′ end of the second amplicon started from the same targeted junction site and extended to a 3′ SalI site downstream of nucleotides encoding the same amino terminus. Oligonucleotide primers were designed with overlaps in the targeted junction region (in bold). This overlap allowed fusion of the two cDNA fragments in a third PCR that used only the 5′ (TGG TTC AGA CTG CAG TGA) and 3′ (TCT AGA GTC GAC CGG G)-flanking primers containing the PstI and SalI restriction sites, respectively. The resulting fusion product was digested with PstI and SalI and substituted for the corresponding PstI/SalI fragment of DN1. The only exception was construction of DN14, which required two independent PCR-SOEing steps (DN14a and DN14b).

**Table I**

<table>
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<tr>
<th>DN</th>
<th>Antisense primer of upstream amplicon</th>
<th>Sense primer of downstream amplicon</th>
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<tr>
<td>DN4</td>
<td>GCA CCA TTT AGT GTC GCC</td>
<td>TAC AGT AAC</td>
</tr>
<tr>
<td>DN5</td>
<td>TTC GTT GAC TGT TGA</td>
<td>GCA ATT TGG ATT</td>
</tr>
<tr>
<td>DN6</td>
<td>GCA CCA TTT AGT GTC GCC</td>
<td>TAC AGT AAC</td>
</tr>
<tr>
<td>DN7</td>
<td>TTC GTT GAC TGT TTT</td>
<td>CTT CCT CAC</td>
</tr>
<tr>
<td>DN8</td>
<td>GCA CCA TTT TGT AGA</td>
<td>GCC ATT TGG ATT</td>
</tr>
<tr>
<td>DN9</td>
<td>TGC TTC ATG AGA TGA</td>
<td>ATC GCC TCT GAA</td>
</tr>
<tr>
<td>DN10</td>
<td>GCG CCA GGC GGC ATC</td>
<td>GTC TTA GAA</td>
</tr>
<tr>
<td>DN13</td>
<td>ATG GCA CCA TTT GGG GGC</td>
<td>ATC GCA TTT</td>
</tr>
<tr>
<td>DN14a</td>
<td>GGC CAG CCA TTT GGG GGC</td>
<td>ATC GCA TTT</td>
</tr>
<tr>
<td>DN14b</td>
<td>GGC CAG CCA TTT GGG GGC</td>
<td>ATC GCA TTT</td>
</tr>
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</table>

PCR that used only the 5′ (TGG TTC AGA CTG CAG TGA)- and 3′ (TCT AGA GTC GAC CGG G)-flanking primers. The resulting fusion product was digested with PstI and SalI and substituted for the corresponding PstI/SalI fragment of DN1. The only exception was construction of DN14, which required two independent PCR-SOEing steps (DN14a and DN14b).

**Expression of Recombinant FN isoforms and Matrix Structure**

Expression and Purification of Recombinant FN Isoforms—Construction of recombinant baculovirus containing the rat V C1 construct has been described previously (26). Full-length (V + C) FN cDNA was subcloned into the baculovirus vector PVL 1392 (BD Pharmingen). Recombinant viruses were generated according to established procedures (27). To produce recombinant protein, 50% confluent T175 flasks of SF21 cells that had been adapted for growth under serum-free conditions (gift from Dr. Ping Wang at Cornell University) were incubated with recombinant viruses for 2 h in Excell-400 medium (JRH Biosciences, Lenexa, KS). After re-feeding, conditioned media from infected cells were collected 48 h later and clarified by centrifugation (175 × g). The mixture of protease inhibitors (above) was added to inhibit proteolysis. Recombinant FN proteins were purified using affinity chromatography columns of gelatin-agarose (Amersham Biosciences), followed by heparin-agarose (Pierce) as described by Poulouin et al. (28). The concentration of purified FN was determined by enzyme-linked immunosorbent assay using a polyclonal (goat) antiserum to human FN, followed by peroxidase-conjugated rabbit anti-goat IgG (ICN Pharmaceuticals Inc.) as described previously (29).

Matrix Structure—FN null mouse embryonic fibroblasts (30) were a gift of Dr. Deane Mosher (University of Wisconsin, Madison). The fibroblasts were plated into the wells (3 × 105 cells/well) of immunofluorescence slides (Polysciences, Warrington, PA) in Dulbecco’s modified Eagle’s medium supplemented with 10% FN-depleted bovine serum (31), glutamine (0.29 mg/ml), and penicillin (100 units/ml)/streptomycin (100 μg/ml). After a 3-h period for cell attachment and spreading, media were removed, and the cells were re-fed with Dulbecco’s modified Eagle’s medium containing 30 μg/ml of either rat plasma FN (pFN, Sigma), recombinant V C1-FN, or recombinant (V + C) C1-FN. The cellular assembly of a FN matrix was allowed to proceed for 24 h.

For immunofluorescence microscopy, cells were fixed with 75% (v/v) paraformaldehyde for 15 min at 4 °C and incubated sequentially with a monoclonal antibody against rat FN (IC-3) in Tris-buffered saline containing 0.1% bovine serum albumin overnight at 4 °C and goat anti-mouse IgG conjugated to fluorescein isothiocyanate (Molecular Probe, Eugene, OR) overnight at 4 °C. After rinses, the slides were covered with glycerol-anti-fade mounting medium (Molecular Probe). The pattern of fluorescence was assessed with an Olympus IX70 confocal microscope using an argon laser with 488 nm excitation and bandpass filters for collecting green fluorescence.

**RESULTS**

Segment I-10 Influences FN Heterodimerization Patterns—Unlike the V C1 and V C0 FN isoforms that can heterodimerize efficiently with each other, the cartilage-specific (V + C) C1-FN isoform exists predominantly as homodimers within canine...
articulate cartilage (13). This dimerization pattern of (V + C)' FN is retained in experimental cell culture models (13) and led to the hypothesis that absence of the III-15 and/or I-10 protein segments restricts heterodimerization with the other two V-region splice variants (V'C' or V'C'). To test the hypothesis, an experimental system using truncated versions of FN,
Role of Segment I-10 in Fibronectin Heterodimerization

A. 

Cells Transfected with

- DN1 + DN6
- DN6/DN6
- DN7
- DN7/DN7
- DN1/DN1
- DN1/DN7
- DN1/DN5
- FN1/FN1
- FN1/DN5

B. 

<table>
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<tr>
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<tbody>
<tr>
<td>DN-2</td>
<td>54.2% ± 4.7%</td>
<td>45.8% ± 4.7%</td>
<td>0</td>
</tr>
<tr>
<td>DN-3</td>
<td>49.5% ± 10.4%</td>
<td>0</td>
<td>50.5% ± 10.4%</td>
</tr>
<tr>
<td>DN-4</td>
<td>25.4% ± 8.8%</td>
<td>3.5% ± 0.4%</td>
<td>71.2% ± 9.2%</td>
</tr>
<tr>
<td>DN-5</td>
<td>22.2% ± 2.0%</td>
<td>48.4% ± 2.1%</td>
<td>29.4% ± 3.9%</td>
</tr>
<tr>
<td>DN-6</td>
<td>54.7% ± 5.1%</td>
<td>0</td>
<td>45.3% ± 5.1%</td>
</tr>
<tr>
<td>DN-7</td>
<td>24.2% ± 8.5%</td>
<td>63.1% ± 4.2%</td>
<td>12.7% ± 11.8%</td>
</tr>
<tr>
<td>DN-8</td>
<td>60.2% ± 2.5%</td>
<td>0</td>
<td>39.8% ± 2.5%</td>
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A Full length FN-1 was substituted for DN-1 to enable band resolution by SDS-PAGE.

Fig. 2. DN1 (or FN1), representing the V+C+ isoform, displays variable heterodimerization potential with other DN constructs. A. conditioned culture media from COS-7 cells following transient transfection with the indicated cDNA construct(a) were analyzed by SDS-PAGE and immunoblotting. Panel a, DN1 does not form heterodimers with DN6. They remain as their corresponding homodimers following co-transfection (lane 2). Lanes 1 and 3 indicate DN1 and DN6 homodimers, respectively. Panel b, DN1 heterodimerizes efficiently with DN7. Co-transfection results in a large amount of DN1/DN7 heterodimers (lane 5). Lanes 4 and 6 illustrate DN1 and DN7 homodimers, respectively. Panel c, FN1 heterodimerizes with DN5. Co-transfection of FN1 and DN5 generates high levels of intermediate-sized FN1/DN5 heterodimers (lane 8). Lanes 7 and 9 indicate single transfections of FN1 and DN5, respectively. B, relative homodimer and heterodimer percentages (mean ± S.D.) determined from immunoblots by either direct quantification of chemiluminescence or decay events from 35S-labeled secondary antibody. DN1 heterodimerizes very inefficiently with DN3, DN6, and DN8, whereas it heterodimerizes efficiently with DN2 and DN7. Homodimers and/or heterodimers from co-transfection of DN1/DN4 and DN1/DN5 could not be resolved by 6% SDS-PAGE. Therefore, full-length V+C+ FN-1 was substituted and used for the DN4 and DN5 analyses.
III-15 does not influence substantially whether heterodimerization is favored with DN3 or DN1.

Importance of a Balanced Number of Type I Repeats at the Carboxyl Terminus

Is there something specific about protein segment I-10 that regulates the heterodimerization patterns of DN1 and DN3, or is it simply necessary to have a balanced number of type I repeats at the carboxyl terminus? For example, it could be necessary to have the same number of carboxyl-terminal type I repeats on each monomeric FN subunit for efficient interchain association or as structural elements for proper alignment. To answer this question, DN9 and DN10, which delete I-11 and I-12 protein segments, respectively, were prepared (Figs. 1 and 4B). DN4, DN9, and DN10 all contain V and III-15, but each has a different combination of two type I repeats at the carboxyl terminus. These constructs were co-transfected individually with DN3 into COS-7 cells. The results are shown in Fig. 4. If a balanced number of type I repeats at the carboxyl terminus determines heterodimerization efficiency, then DN3 would be expected to form similar amounts of heterodimers with DN4, DN9, and DN10. Although DN3 does not heterodimerize with DN1 and DN5 but demonstrates variable heterodimerization potential with the other DN constructs.

TABLE II

Summary of the dimerization patterns of DN1 and DN3 with co-transfected DNs

The presence or absence of V, III-15, and I-10 protein segments in the various DN constructs is indicated by the + or − sign. Relative dimerization efficiencies (from Figs. 2B and 3B) were scored in deciles by asterisks as indicated. Percent heterodimerization of DNs: *, 0–10%; **, 11–20%; ***, 21–30%; ****, 31–40%; ***** 41%. The data demonstrate the following: 1) a DN that lacks protein segment I-10 heterodimerizes preferentially with DN3, which also lacks the I-10 segment; 2) a DN that includes the I-10 segment heterodimerizes preferentially with DN1 (or FN1), which also includes the I-10 segment; and 3) the presence or absence of protein segment V and III-15 does not influence substantially whether heterodimerization is favored with DN3 or DN1.

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<tbody>
<tr>
<td>DN1</td>
<td>50.5% ± 10.4%</td>
<td>0</td>
<td>49.5% ± 10.4%</td>
</tr>
<tr>
<td>DN2</td>
<td>68.7% ± 6.6%</td>
<td>16.2% ± 4.6%</td>
<td>16.1% ± 2.1%</td>
</tr>
<tr>
<td>DN4</td>
<td>32.3% ± 1.3%</td>
<td>39.9% ± 1.9%</td>
<td>27.8% ± 2.9%</td>
</tr>
<tr>
<td>DN5</td>
<td>57.7% ± 10.0%</td>
<td>0</td>
<td>42.3% ± 10.0%</td>
</tr>
<tr>
<td>DN6</td>
<td>36.3% ± 3.7%</td>
<td>35.4% ± 1.2%</td>
<td>28.4% ± 3.9%</td>
</tr>
<tr>
<td>DN7</td>
<td>32.1% ± 3.6%</td>
<td>33.7% ± 3.5%</td>
<td>34.3% ± 2.8%</td>
</tr>
<tr>
<td>DN8</td>
<td>47.8% ± 3.9%</td>
<td>27.8% ± 4.3%</td>
<td>24.4% ± 0.4%</td>
</tr>
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* Full-length FN-1 was substituted for DN-1 to enable band resolution by SDS-PAGE.
DN13 and DN14 were constructed to enable a parallel analysis with DN1. They are structurally similar to DN7, all three lacking V and III-15, but segment I-10 is removed and substituted with duplications of either I-11 (DN13) or I-12 (DN14) (Figs. 1 and 5B). As reported in Fig. 5, these changes greatly reduce the formation of DN1 heterodimers. Once again, efficient heterodimerization of different DN isoforms requires that both subunits have the same I-10 status. In this case, both DN1 and DN7 contain protein segment I-10 and heterodimerize most efficiently.

**FN Matrix Structure**—The unique primary structure and restricted heterodimerization of (V + C)⁻ FN raise the potential that this isoform may have different matrix assembly characteristics that influence the matrix organization and biomechanical properties of cartilage. To explore this possibility and compare FN matrix structure, pFN, recombinant V⁺C⁺ FN, and recombinant (V + C)⁻ FN (30 µg/ml) were added to mouse embryonic fibroblasts that lack endogenous FN expression. Matrix assembly was allowed to proceed for 24 h. Immunofluorescence microscopy indicated that all three FN preparations are able to be assembled into a matrix and have similar linear arrays of fibrils (Fig. 6). Compared with pFN and V⁺C⁺ FN, the fibrils of the (V + C)⁻ FN are subjectively less extensive (Fig. 6, A–C). At higher magnification, however, no differences in either the pattern or the thickness of fibrils are appreciated (Fig. 6, D–F).

**DISCUSSION**

The cartilage-specific FN isoform, (V + C)⁻, is expressed predominantly in homodimeric configurations both within native cartilaginous tissues and in experimental cell culture systems (13). Heterodimers between the (V + C)⁻ FN and other V-region splice variants (V⁺C⁻ or V⁻C⁺) are either not observed or detected at only low levels. This is not due to a problem with secretion, rather it is that (V + C)⁻ FN heterodimers simply are not produced efficiently by either chondrocytes or transfected cell lines. In this report, we tested the hypothesis that lack of the III-15 and/or I-10 protein segments in (V + C)⁻ FN restricts its ability to heterodimerize with other V-region splice variants. By constructing truncated DNs with various deletions of the V, III-15, or I-10 segments and co-transfecting them with either DN1 (V⁺C⁻ DN) or DN3 ((V⁻C⁺)⁻ DN), we have shown that heterodimerization occurs with increased efficiency when the two monomeric subunits either both contain protein segment I-10 or both have segment I-10 deleted (data summarized in Table II). Levels of heterodimerization are reduced when one subunit contains I-10 and the other lacks I-10. Based on this relationship, the absence of protein segment I-10 in (V + C)⁻ FN appears to explain why this isoform is not found in heterodimeric configurations with the other native V-region splice variants within cartilage.

Analyses of FN dimers by high performance liquid chromatography (2) and nuclear magnetic resonance spectroscopy (3) reveal that the two monomeric subunits are linked in an antiparallel fashion. Two coiled segments at the carboxyl terminus, each composed of only four amino acids, may serve as local interchain recognition sites (4). Although not an absolute structural determinant of dimerization, two monomeric subunits that match in terms of the presence or absence of segment I-10 may be more efficient at achieving the alignment that is necessary to bring the carboxyl-terminal cysteine pairs and adja-
cent coiled segments into close proximity with an anti-parallel orientation prior to disulfide bond formation. Alternatively, conformational relationships mediated by segment I–10 may allow efficient binding of protein-disulfide isomerase (32–35) or interactions with protein segment I–12 of FN that has been shown to have intrinsic protein-disulfide isomerase activity (36). The formation and rearrangement of intra- and intermolecular disulfide bonds mediated by protein-disulfide isomerase are critical to the stabilization of FN dimers and multimers. As with other enzymes, the catalytic capability of protein-disulfide isomerase is related to its ability to bind substrates and stabilize the intermediate enzyme-substrate complexes (37–40). In support of the current data, studies by other groups (19, 41) have also suggested that the three type I repeats at the carboxyl terminus may have important functional roles in dimerization related to interchain associations and disulfide-bond formation. Deletional mutants of FN lacking segments I–10 through I–12 or III–15 and I–10 through I–12 failed to heterodimerize with endogenous mouse FN when stably expressed in mouse L cells, although they retained the ability to form homodimers (19). Additionally, Sottile and Mosher (41) found that only 30% of FN deleting I–10 through I–12 segments was...
dimeric as compared with 60% for endogenous COS cell FN. Considering the findings of these two papers and the data presented in Figs. 1 and 2 of the current study, an important issue is whether segment I-10 specifically plays an important role in FN dimerization. Another possibility is that I-10 is no more important than I-11 or I-12 in this context. Each monoclonal subunit may only need to have the same number of type I repeats at the carboxyl terminus for efficient dimerization.

Addressing this question using the V⁺C⁺ isoform as represented by DN1, segment I-10 appears to be critical. Deleting I-10 but maintaining a total of three type I repeats carboxyl terminus by duplicating either I-11 (DN13) or I-12 (DN14) reduced heterodimer formation with DN1 to near zero (Fig. 5). A similar relationship was observed with the (V⁺C⁺) isoform (Fig. 4), but the constraints were not absolute. DN3/DN9 and DN3/DN10 heterodimerization did occur, albeit at significantly lower levels. These data do not indicate that a balanced number of type I repeats at the carboxyl terminus of each FN monomer is not a variable that influences dimerization efficiency; we think it probably is a variable. Rather, segment I-10 appears to have a role over and above this issue by a structural or functional mechanism yet to be determined. Nuclear magnetic resonance spectroscopy of recombinant I-4 and I-5 indicates that these two amino-terminal type I repeats interact structurally. A tryptophan unique to I-4 interacts with an arginine residue in I-5 creating a hydrophobic interface that fixes these two segments in a constrained conformation (42). Similar inter-module interactions involving I-10 might be important for maintaining conformational relationships at the carboxyl terminus that are important for disulfide bonding and FN dimerization.

Different isoforms and dimerization patterns have been shown to influence FN solubility and matrix assembly (1, 16, 57). Release of FN from the cell surface to the extracellular matrix even though segments III-15 and I-10 appear to be critical. Deleting I-10 or functional mechanism yet to be determined. Nuclear magnetic resonance spectroscopy of recombinant I-4 and I-5 indicates that these two amino-terminal type I repeats interact structurally. A tryptophan unique to I-4 interacts with an arginine residue in I-5 creating a hydrophobic interface that fixes these two segments in a constrained conformation (42). Similar inter-module interactions involving I-10 might be important for maintaining conformational relationships at the carboxyl terminus that are important for disulfide bonding and FN dimerization.

References

Acknowledgments—we are grateful to Dr. Jean Schwarzbauer (Princeton University) for the gift of the isoform created by the novel juxtaposition of protein segments III-14 and I-11. The changes are also reflected functionally in terms of altered proteoglycan binding properties (61). Therefore, the unique structural features of the cartilage-specific (V⁺C⁺) FN isoform that change dimerization and the heparin II binding region clearly have the potential to influence matrix organization and contribute to the specialized biomechanical properties of cartilage that provide load distribution and facilitate joint motion.

References

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