Fibronectin: Structure, Assembly, and Cardiovascular Implications

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In the past 2 decades, it has been appreciated that the functions of the extracellular matrix (ECM) are not entirely structural. ECM components interact with specific adhesion receptors on cell surfaces and regulate various cellular functions, including differentiation, proliferation, migration, and apoptosis. Fibronectin (FN) is a paradigm adhesive protein, nonreactive with adhesion receptors in its soluble state but highly adhesive when insoluble. Polymerization of FN into the ECM must be tightly regulated to ensure that the adhesive information in the ECM is appropriate.

FN exists in a soluble protomeric form in micromolar concentration in blood plasma and in an insoluble multimeric form in the ECM.1,2 Unlike fibrillar or basement membrane collagens, laminins, actin, and tubulin, circulating FN does not self-polymerize in physiologically relevant solutions. Furthermore, there is little passive accumulation of FN in preexisting ECM. Rather, assembly of FN takes place at specialized areas on the cell surface.3 FN is especially abundant in the ECM of embryonic and regenerating or injured tissues, although it can be found in most ECMs, including basement membranes. FN interacts with cells through integrins, heterodimeric transmembrane receptors linking the ECM to the intracellular cytoskeleton and signaling pathways. The aim of this review is to describe the mechanisms and consequences of FN deposition and give a brief overview of the significance of FN for selected areas of cardiovascular research. In the first section we describe important features of the FN molecule that account for its multiple functions. Next, we focus on the assembly process, ie, the conversion of soluble FN to its active, adhesive, insoluble form. Finally, we discuss several areas of cardiovascular research in which FN may have an important role, exemplifying how the adhesive information of FN can drive pathophysiological processes.

Structure of FN

Soluble FN is a dimeric glycoprotein. Each subunit is a mosaic of a series of repeating modules: 12 type I modules, 2 type II, 15 to 17 (depending on splicing) type III, and a variable (V) sequence that is not homologous to other parts of FN (Figure 1). The deduced amino acid sequences for FNs of the clawed frog and rat are well conserved, possessing 71% amino acid identity and the same overall organization.4 The 2 type III modules that are subject to alternative splicing are called ED-A (ED for “extradomain”) and ED-B. Plasma FN is synthesized in the liver by hepatocytes and contains neither ED-A nor ED-B, whereas so-called “cellular” FN (synthesized locally in tissues) contains variable amounts of either or both ED-A and ED-B.1,2 Furthermore, in plasma FN dimers, only 1 of the subunits contains the V region, whereas almost all cellular FN subunits contain this region.3

FN binds to $\alpha_\text{IIb}\beta_3$ and $\alpha_\text{VI}\beta_3$ integrins through a cell adhesive site comprising modules III8-III10. The most critical site is the Arg-Gly-Asp (RGD) sequence in III10. RGD peptides block integrin-mediated cell adhesion to FN.3,4 RGD sequences occur in other molecules that mediate adhesion to integrin receptors as well.1,2 The sequence in FN is synergized by modules III8-III9. The Pro-His-Ser-Arg Asn sequence in III9 is of special importance.4,5 The crystal structure of the seventh to 10th type III repeats (III7-III10) reveals an extended rodlike molecule with a long axis of $\approx$140Å and a somewhat variable relationship between adjacent modules. The relationship between III9 and III10 creates a distinctive binding site, in which the RGD loop in III10 and the synergy region from III9 are on the same face of III7-10 and thus, easily accessible to the integrin.8

The FN molecule also has many other adhesive sites for various substances, including fibrin, heparin, collagen, and $\alpha_\text{IIb}\beta_3$ and $\alpha_\text{VI}\beta_3$ integrins (Figure 1). A Gln residue close to the amino terminus serves as a transglutamination site for activated factor XIIIa (fXIIIa); plasma transglutaminase), cross-linking FN to various other proteins, including fibrin, fibrinogen, and itself. Cross-linking by fXIIIa is important for incorporation of FN into fibrin clots during the clotting process.1,2 $\alpha_\text{IIb}\beta_3$ and $\alpha_\text{VI}\beta_3$ integrins recognize a Leu-Asp-Val sequence in the V region of FN.3

Given the developmental and tissue-specific patterns of splicing, it seems very likely that different splice variants have specific cellular effects. Studies on chondrogenesis have shown the ED-A domain to be essential at the level of cellular condensation.10 In an experimental rat hepatic fibrosis model, there was marked increase in ED-A–positive FN expressed in sinusoidal endothelial cells, and the matrixes deposited by these cells stimulate the conversion of liver lipocytes to myofibroblasts.11 This stimulation was blocked by antibodies specific to the ED-A domain, whereas recombinant FN
peptides containing the ED-A domain mimicked the effect. Fibrosarcoma cells have increased adhesion and spreading on recombinantly expressed ED-A– containing FN compared with ED-A–negative FN. Unlike the effects on liver lipocytes, this effect could not be blocked by anti–ED-A antibodies but was blocked by RGD-containing peptides or antibodies against \( \alpha_5 \) and \( \beta_1 \) integrin subunits. Furthermore, purified \( \alpha_5 \beta_1 \) bound more avidly to ED-A– containing FN than ED-A– negative FN, suggesting that the effect of the ED-A exon splicing is to improve binding affinity to integrin.

**FN Matrix Assembly**

FN matrix assembly is a cell-mediated process that occurs in a stepwise manner. Initially, soluble protomeric FN binds to the cell surface via an interaction mediated primarily by the N-terminal 70-kDa region of the protein. This first step is saturable and reversible. In the next step, cell-bound protomeric FN is converted into disulfide-stabilized multimers by interaction among or between FN molecules. In a presumptive final step, the binding site on the cell surface is regenerated. Assembly takes place at specialized sites on cell surfaces and requires the participation of both integrins and cell surface sites referred to as LAMMs (molecules of large apparent molecular mass; see below). Fibroblasts, endothelial cells, vascular smooth muscle cells, and other cell types secrete, bind, and assemble FN into fibrils in the ECM. Plasma FN and cellular FN synthesized locally both have the potential to be deposited into the ECM. Figure 2 schematizes our current understanding of cellular regulation of the assembly process. In this section, we will highlight the important sites in the FN molecule, as well as the cell surface and intracellular regulatory components, involved in FN assembly.

**Regions of FN Important for Matrix Assembly**

There are several regions within FN that have vital importance in the assembly process (Figure 1). Deletion of the 20 amino acids from the carboxyl terminus yields monomeric FN owing to lack of the Cys residues involved in interchain disulfide bridges. This monomeric FN does not become incorporated into the matrix. Most of the binding activity that directs FN to assembly sites is contained in the amino-terminal 70-kDa region (70-kDa fragment), in particular, within modules I1-I5. Although proteolytic fragments or recombinant proteins containing these modules do not assemble into fibrils, these proteins bind to assembly sites with the same avidity as intact FN and block the binding and assembly of intact FN. Use of the 70-kDa fragment has proved valuable in studying the regulation and characteristics of the cell surface assembly sites. Removal of any of the modules I1-I5 results in a protein with markedly decreased affinity for assembly sites, and similarly, mutations of conserved Tyr residues in any of the modules cause decreased affinity. It is likely that the 5 type I modules work as a single functional unit in binding to the cell surface. Two other regions, the presumptive self-interacting site II9/III1 and the cell adhesion site III8-10, also appear to be important in the assembly process, although controversy still remains about their exact role. The III1 module has been shown under denatured condition to bind the 70-kDa fragment. Furthermore, the cell adhesive III10 module has been shown to bind III1 in an RGD-independent manner. By immunofluorescence, the 70-kDa fragment colocalizes with III1 and III10 modules when added to fibroblasts under serum-free conditions. These results raise the possibility that the matrix assembly site, ie, the 70-kDa-fragment binding site, is cryptic within module III1, and binding of this module to III10 might expose the
70-kDa binding site, thus allowing assembly to occur. Against this hypothesis are the inability to cross-link the 70-kDa fragment to preexisting FN with IXIIIa under conditions favoring the binding of 70-kDa fragment to the cell surface (see below) and the lack of good colocalization of the 70-kDa fragment with preexisting FN.\(^{24}\)

**Role of Integrins**

Among the membrane components involved in FN polymerization, integrins have been shown to play an important role. Integrins are heterodimeric transmembrane receptors that mediate organization of focal contacts, actin-containing cytoskeleton, and ECM. Transfection of \(\alpha_5\) integrin and expression of \(\alpha_5\beta_1\) integrin in Chinese hamster ovary (CHO) cells result in a large increase in FN assembly.\(^{25,26}\) A chimera comprising the interleukin-2 receptor and the cytoplasmic tail of \(\beta_1\) functions in a presumptive dominant-negative manner to inhibit assembly.\(^{27}\) Monoclonal antibodies to \(\alpha_5\) or \(\beta_1\) inhibit binding and assembly of FN by fibroblasts and also binding of the N-terminal FN fragment to cell surfaces.\(^{28,29}\) The 70-kDa fragment of FN that mediates binding to assembly sites colocalizes with \(\beta_1\) integrin in focal contacts.\(^{30}\) However, cell surface \(\alpha_5\beta_1\) integrin could not be demonstrated to bind to the N-terminal 70-kDa fragment by affinity chromatography.\(^{29}\) Furthermore, studies of \(\alpha_5\) knockout mice and cells derived from these mice and also of \(\beta_1\) knockout cells\(^{31,32}\) indicate that other molecules can substitute for \(\alpha_5\beta_1\) in matrix assembly.

Expression of activated forms of \(\alpha_5\beta_1\)\(^{33,34}\) and \(\alpha_5\beta_3\)\(^{35}\) allows CHO cells to assemble an FN matrix. Overexpression of \(\alpha_5\), which can pair with \(\beta_1\) or \(\beta_3\),\(^{36}\) or \(\alpha_5\), which pairs with \(\beta_1\),\(^{37}\) does not confer assembly competency to CHO cells. Transfection of \(\alpha_3\) causing overexpression of \(\alpha_3\beta_1\), an adhesion receptor for entactin, allows assembly of FN if CHO cells are cultured on an entactin-coated substrate; such assembly is not blocked by antibodies to the cell adhesion domain of FN.\(^{38}\) Cells with blocked protein synthesis\(^{30}\) or those lacking \(\beta_1\) integrins\(^{39}\) are unable to assemble FN when cultured on vitronectin. Thus, expression of several different integrins allows adherent cells to be assembly-competent, and the specific integrins required seem dependent on the substrate to which assembling cells are adherent. Ligated integrins probably signal, at least in part, through activation of Rho-dependent pathways\(^{40,41}\) that appear to play an important role in the assembly process (see below).

**Role of Actin Stress-Fiber Formation, Cell Contraction, and LAMMs**

Serum and lipoproteins stimulate FN matrix assembly by MG63 osteosarcoma cells and normal fibroblasts.\(^{42,43}\) More recently, the phospholipid growth factor lysosphosphatidic acid (LPA), abundant in serum and lipoproteins, has been shown to mediate this effect.\(^{44}\) LPA is a product of activated platelets and has diverse actions on cells mediated by activation of several signal transduction pathways.\(^{45}\) The enhanced binding is due to increases in both the number and affinity of cell surface binding sites. The increase in binding sites induced by LPA is labile; the sites rapidly disappear when LPA is removed and reappear when LPA is added again. The binding also correlates with changes in cell shape and actin-containing cytoskeleton.\(^{44}\) On scanning electron photomicrographs, the binding sites for FN on LPA-stimulated cells occur on areas of the cell membrane containing numerous cell protrusions that extend between cells or between cells and the substratum.\(^{44}\)

Disruption of microtubules has been shown to mimic some of the intracellular effects of LPA, including the formation of actin stress fibers and myosin light-chain phosphorylation.\(^{46,47}\) Disruption of microtubules by nocodazole or vinblastine increases both the number and affinity of binding sites on cells, and the modulation is rapid, dynamic, and reversible.\(^{48}\) These effects are identical to the effects of LPA on FN binding. Another agent that mimics the cytoskeletal effects of LPA is the sphingolipid sphingosine-1-phosphate. This agent also causes rapid upregulation of FN binding sites (Q. Zhang et al, unpublished data, 1997).
Fluorescence microscopy has revealed a close correlation among actin stress-fiber formation, cell contraction, and FN binding in all of the stimulatory agents tested, indicating that upregulation of the matrix assembly sites is secondary to actin stress-fiber formation and cell contraction. At nanomolar concentrations, LPA stimulates rapid formation of actin stress fibers mediated by activation of the small GTP-binding protein Rho in fibroblasts. The enhanced binding of soluble FN and the 70-kDa fragment is seen with similar doses of LPA. Rho-mediated actin stress-fiber formation is dependent on activation of the actin-myosin contractile apparatus. Blockage of the small GTP-binding protein Rho, myosin light-chain kinase, or actin-myosin interactions inhibits the effects of both nocodazole and LPA on FN binding. These observations demonstrate that Rho-dependent actin stress-fiber formation and cell contraction induce increased FN binding and represent a rapid, labile way that cells can modulate FN matrix assembly.

Two different cross-linking strategies have been used to identify the cell surface molecules on adherent cells that bind FN or its 70-kDa fragment as LAMMs on SDS–polyacrylamide gel electrophoresis. No evidence was found for cross-linking to integrins or, surprisingly, endogenous FN. Cross-linking to LAMMs is subject to tight modulation, as befits the labile nature of the assembly site. Treatment with LPA or microtubule disruption induces tension on the adherent cells and may stretch labile assembly sites, leading to exposure of multiple, cryptic binding sites for the N-terminal modules of FN.

Cellular display of FN matrix assembly sites, in conclusion, is labile and correlates with cell shape change and cytoskeleton organization as illustrated in Figure 2. Integrins play important roles in FN deposition by sensing information from the ECM and influencing cytoskeletal organization and cell shape and perhaps also by concentrating assembling FN molecules. Cell surface LAMMs are present at the labile assembly sites for FN. Cellular display of assembly sites requires that cells be under tension and is tightly regulated. Another way of achieving insolubilization is cross-linking of soluble FN to already-formed matrix, best exemplified in the blood clotting process. This process is discussed in the next section.

**FN and the Cardiovascular System**

**FN and Blood Clotting**

The conversion of fibrinogen to fibrin and formation of the fibrin clot are the culminating events in the blood clotting process and are under tight control, just like the insolubilization of FN. The pathway of blood clotting is very different from the pathways described above for FN, the most obvious differences being the lack of proteolytic processing of FN. Interestingly, though, blood clotting is initiated by a cell surface protein, tissue factor, and the cross-linking by fXIIIa is common to the 2 pathways.

After tissue injury, formation of a blood clot serves the dual role of restoring vascular integrity and serving as a temporary scaffold for the wound healing process. It has long been known that improper wound healing occurs in fXIII-deficient patients and that fibroblast growth is impaired in clots formed from fXIII-deficient plasma. fXIIIa covalently cross-links fibrin molecules to greatly increase the structural stability. Furthermore, fXIIIa catalyzes cross-linking of soluble FN to the fibrin clot. Cross-linking occurs through the formation of covalent bonds between Gln residues in the N-terminal region of FN and the ε-amino group of a Lys residue in the α-chain of fibrin. The covalently cross-linked FN further enhances the stability of the clot. Plasma FN is preferred over cellular FN in this cross-linking process, apparently because of the asymmetric distribution of the V region in only 1 of the 2 subunits of the plasma FN dimer. The cross-linking of FN to the fibrin clot promotes fibroblast adhesion and spreading, such that cross-linked FN is an absolute requirement for migration of fibroblasts into plasma clots formed in vivo. When FN with engineered mutations of the Gln residues involved in cross-linking is used in vitro clot formation, adhesion and spreading of fibroblasts are markedly reduced. Thus, cross-linking of soluble FN to fibrin must expose the adhesive domains for cellular interactions in a way that attracts the fibroblasts into the clot.

Fibroblasts in the healing wound acquire a phenotype called the myofibroblast, important for wound contraction. It is these tension-generating cells that assemble FN. The wound healing process is thus initiated by the proteolytic blood clotting process, which, owing to the cross-linking of FN to the clot, enables the migration of the cellular elements of wound healing to the area. The cells acquire a phenotype suitable for further assembly of FN matrix, which finally is replaced by collagen as the wound heals. FN can also be cross-linked to collagen, a reaction that is potentially important for collagen fibrillogenesis. A schematic model of the sequential matrix deposition in wound healing is depicted in Figure 3. This model of matrix deposition seems to hold true in a variety of tissue injuries. The first step, ie, fibrin deposition, is dependent on activation of the blood clotting system and is seen only when vascular integrity is altered. FN deposition (late provisional matrix) can be seen in a wide variety of tissue reparative processes and portends more permanent collagen deposition. Examples of this are discussed below with regard to vascular and myocardial processes. It is likely that the adhesive information within the insoluble FN is more important than its structural role. The ability of FN to attract fibroblasts into the wound healing area and alter their gene expression and phenotype seems central to its importance in this process.

FN as a ligand for platelet integrins may also be involved in platelet adhesion and aggregation. FN binds to the platelet integrins αIIbβ3 in an activation-dependent manner and to αIβ2 in an activation-independent fashion. Under shear stress in an ex vivo system, platelets deposit with similar efficiencies to surfaces coated with FN, fibrinogen, or von Willebrand factor (vWF). Although adhesion to FN depends on binding to αIIbβ3 and αIbβ2 in an RGD-sensitive manner, under shear stress, adhesion to FN is also dependent on glycoprotein Ib adhesion via vWF. Platelet aggregation can proceed normally in FN-depleted plasma, but because the platelets themselves contain FN in the α-granules, it is difficult to exclude a role for FN in this process. Furthermore,
a monoclonal antibody against platelet FN inhibits platelet aggregation while having no effect on serotonin release. Thus, although fibrinogen and vWF are the major ligands for platelet adhesion and aggregation, it is likely that FN plays more than a cameo role.

**FN and Atherosclerosis**

The highly organized histological architecture of the vascular wall and the specialized cellular phenotypes are perturbed in conditions like atherosclerosis, restenosis, and hypertension. In atherosclerosis, the change in phenotype of the endothelial lesion is postulated to play a key role in initiation and progression of the atherosclerotic lesion. In the more advanced lesion, the location and phenotype of the vascular smooth cell are markedly altered. Smooth muscle cells acquire a proliferative, synthetic phenotype and migrate into the subendothelial lesion. The proliferative phenotype is characterized by a change in protein expression, increase in response to growth factors, and formation of extensive rough endoplasmic reticulum and a large Golgi complex. Increased expression of FN may contribute to the transformation of vascular smooth muscle cells in intimal thickening of atherosclerotic lesions, from the contractile phenotype to a synthesizing or proliferative phenotype. One of the striking differences that occurs in the vascular wall is a change in the composition of the ECM. Under normal conditions, the main components of the matrix proteins are basement membrane proteins, collagen type IV, and laminin. Significant amounts of FN are also found, but such FN is strictly devoid of the ED-A and ED-B domains. In atherosclerotic lesions, there is a marked increase in FN that colocalizes with collagen type III, which is also upregulated. This pattern suggests a tissue repair–type process analogous to that which can be observed during wound healing. When studied in vitro, vascular smooth cells can be induced to switch back and forth between the 2 phenotypes, depending on the matrix on which the cells are grown. The basement membrane components laminin and collagen type IV promote the contractile phenotype, whereas FN promotes the synthetic phenotype. After experimental endothelial denudation, there is rapid (24 to 48 hours) upregulation in the expression of FN mRNA, including both ED-A– and ED-B–positive isoforms. This expression is sustained even after reendothelialization is achieved. Similarly, after vascular injury, immunoelectron microscopy studies in vivo show a close association between deposition of FN and the synthetic phenotype, whereas laminin and other basement membrane components are associated with a contractile phenotype.

Based on data with angiotensin II type 1 receptor antagonists and infusion of angiotensin II, it has been postulated that angiotensin II plays an important role in the neointimal thickening after vascular injury. Furthermore, blocking the angiotensin II receptor significantly inhibits mRNA expression of immediate-early genes (c-fos, c-jun, and Egr-1) and FN as well as inhibiting FN protein deposition after arterial injury. Inhibition of expression is associated with a decrease in the overall intimal thickening. Taken together, these data indicate that FN expression is closely associated with the development of atherosclerosis and that the isoform expression includes the ED-A and ED-B forms not normally seen in the adult vessel wall. Although it is not definite whether the ED-A or ED-B splice variant plays a specific role in promoting the changes seen in vascular smooth cells, given the developmental and tissue-specific patterns of splicing, it seems very likely that these different splice variants have specific cellular effects, as discussed above.

**FN and Hypertension**

Vascular smooth muscle cells in hypertensive subjects exhibit a phenotype similar to that seen in the atheromatous lesion. This proliferative phenotype is closely associated with a marked upregulation in ED-A–positive FN. Furthermore, hypertension in different rat animal models has been shown to rapidly increase ED-A–positive FN expression (3- to 6-fold), correlating with the degree of blood pressure elevation; this expression is reversed by normalization of the blood pressure. Similar to FN expression in atherosclerosis, angiotensin II rapidly increases FN expression in the aortic wall after a 3-day infusion, an effect that is inhibited by angiotensin II receptor blockade and occurs independently of the increase in blood pressure.

The end-organ damage seen in the heart in hypertension is characterized by a marked increase in FN expression. The left ventricular hypertrophy characteristically seen in hypertension is associated with an abnormal accumulation of fibrillar collagen. This deposition is thought to account for the myocardial stiffness central to the myocardial dysfunction in hypertensive heart disease. The cardiac interstitial fibroblasts and/or pericytes acquire a myofibroblast phenotype similar to that described for wound repair. Before the deposition of collagen in the hypertensive myocardium, there is an increase in FN mRNA expression and FN deposition.
This FN is predominantly ED-A– and ED-B–positive. A role for angiotensin II in inducing the gene expression necessary for tissue repair is postulated to be central and might explain the multiple beneficial effects of angiotensin-converting enzyme inhibitors on cardiac remodeling and hypertrophy. Angiotensin-converting enzyme inhibitors inhibited the accumulation of FN in the hypertensive myocardium, even at a low dosage that did not alter blood pressure.

**FN and Myocardial Infarction**

Myocardial infarction is a prime example of the importance of the wound healing process. The formation of the scar and the remodeling of the myocardial wall are major determinants of patient outcome. As expected, FN is rapidly expressed after myocardial infarction in both human and animal models. This increase in FN involves both ED-A and ED-B–positive and –negative FN and occurs with or without reperfusion, although there are trends toward increased FN expression after delayed reperfusion.

**Future Directions**

The understanding of the interactions between cells and the ECM has suggested strategies to intervene in disease pathogenesis. Although much of the impetus to disrupt interactions between the ECM and integrins has focused on the design of antitumor therapies, it has been in the field of cardiovascular diseases that the strategy first reached fruition. Humanized mouse monoclonal antibody against α₁β₅ efficiently blocks fibrinogen-dependent platelet aggregation and is beneficial in preventing acute thrombosis after angioplasty. Given the complexity of control of both FN deposition and the cellular consequences of adhesion to FN, additional strategies that target FN deposition pathways specifically may yield additional beneficial effects.

Many questions are unanswered regarding the role of increased FN deposition in various cardiovascular disease processes. The role of the various splice variants of FN, eg, in mediating the phenotypic transformation of vascular smooth cells, needs elucidation. The effects of angiotensin and its inhibitors on deposition of FN by smooth muscle cells and cardiac fibroblasts need to be assessed. Finally, more needs to be learned about the impact of lipid mediators such as LPA on the pathogenesis of cardiovascular diseases.

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**References**


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