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Research Article

# FIBRONECTIN: STRUCTURE AND POSSIBLE FUNCTIONS-A REVIEW

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**A R T I C L E I N F O**

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**A B S T R A C T**

**Aim and objective:** The purpose of this review is to illustrate the structure and possible functions of fibronectin.
**Background:** Fibronectin (FN) is a ubiquitous extracellular matrix (ECM) glycoprotein that plays vital roles during tissue repair. Fibronectin (FN) mediates a wide variety of cellular interactions with the extracellular matrix (ECM) and plays important roles in cell adhesion, migration, growth and differentiation. FN is widely expressed by multiple cell types and is critically important in vertebrate development, as demonstrated by the early embryonic lethality of mice with targeted inactivation of the FN gene. Although FN has been studied for more than two decades, this remarkably complex molecule is still the subject of exciting discoveries, such as finding new integrin and heparin-binding sites or even a new form of the molecule



## INTRODUCTION

Fibronectin is a ubiquitous glycoprotein that plays vital roles during tissue repair. FN is a large glycoprotein that has been implicated in a wide variety of cellular properties, particularly those involving the interactions of cells with extracellular materials. These properties include cell adhesion, morphology, cytoskeletal organization, migration, differentiation, oncogenic transformation, phagocytosis and haemostasis. FN is widely expressed by multiple cell types and is critically important in vertebrate development, as demonstrated by the early embryonic lethality of mice with targeted inactivation of the FN gene. Fibronectin usually exist as a dimer composed of two nearly identical 250kDa subunits linked covalently neat their c-termini by a pair of disulfide bonds. [Figure1] Each monomer consist of three types of repeating units (termed FN repeats): type I, type II and type III. FN contains 12 type I repeats, two type II repeats and 15-17 type III repeats, which together account for approximately 90% of the FN sequence. Type I repeats are about 40 amino-acid residues in length and contain two disulfide bond; type II repeats comprise a stretch of approximately 60 amino-acids and two intra-chain disulfide bonds; and type III repeats are about 90 residues long without any disulfide bonds.[1] Although FN molecules are the product of single gene, the resulting protein can exist in multiple forms that arise from alternative splicing of a single highlight potential strategies whereby fibronectin deposition, engagement with cell surface receptors and activation of cell signalling pathways may be exploited to halt tumour progression. In this manner, it is with anticipation that a new generation of novel therapeutics may be developed to better combat fibronectin's participation in tumorigenesis.

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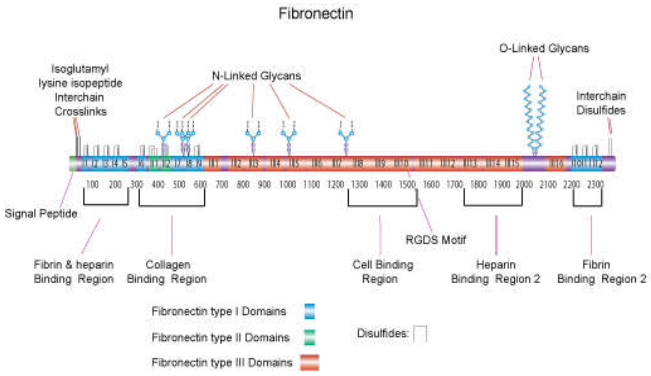


**Figure 1**

### *Source and Production of Fibronectin*

In vivo, fibronectins are found in body fluids (300 µg/ml in plasma, lesser amounts in other fluids), soft connective tissue matrices, and most basement membranes. Fibronectin is produced by a wide variety of epithelial and mesenchymal cells in vitro including: fibroblasts, chondrocytes, myoblasts, Schwann cells, macrophages, hepatocytes and intestinal

epithelial cells. Cellular fibronectin is present in many tissues including spleen, lymph node, tonsil, blood vessel walls, liver, kidney, muscle, skin, brain and peripheral nerves. It is found in basement membranes and in loose connective tissue stroma. It is also present in platelet α-granules and is expressed on the platelet surface after activation. There are at least two types of fibronectin termed plasma and cellular fibronectins, although there may well be multiple forms of cellular fibronectin. Cellular and plasma fibronectins, although distinguishable, are very similar in structure and properties. One major source of plasma fibronectin appears to be hepatocytes x although endothelial cells and macrophages could also contribute, given their close association with the bloodstream.

Source of fibronectin solution, liquid and lyophilized powder is from bovine plasma, can be stored in 2-8°C, source of fibronectin powder is from rat plasma and can be stored in -20 degree c; Superfibronectin solution is taken from human plasma and escheria coli, its storage temperature is 2-8°C. Source of fibronectin like protein polymer,lyophilized powder and fibronectin like engineered protein polymer plus powder is genetically engineered. The target cells for the fibronectins to get attachment are: epithelial cell, mesenchymal cells, neuronal cells, neral crest cells and endothelial cells.[3]

***Plasma Fibronectin***

Plasma fibronectin was originally described as a nonthrombin coagulable by-product of fibrinogen-rich plama fractions. The protein then known as CLg was extensively characterized by Mosesson and collegues in the 1970s. Fibronectin is a significant plasma protein in vertebrates. In man, plasma fibronectin concentration range from approximately 200-700pg/ml. Plasma FN is synthesized by hepatocytes and secreted into the blood plasma, where it circulates at 300-400 μg/ml [4] in a soluble, compact, inactive form. In soluble plasma FN, only one subunit possesses a V domain, and the EIIIB and EIIIA modules are absent [5]. Only very low levels (1.3-1.4 μg/ml) of FN possessing the EIIIA and/or EIIIB modules (cellular FN) have been reported to circulate in the blood plasma [6], but blood plasma levels have been shown to increase after major trauma resulting in vascular tissue damage, after inflammation, and in diseases such as atherosclerosis, ischaemic heart disease and stroke [7].

***Cellular Fibronectin***

Cellular fibronectin refers to the form of the protein present in tissue and in pericellular matrix of cultured fibroblasts. Cellular FN is synthesized by many cell types, including fibroblasts, endothelial cells, chondrocytes, synovial cells and myocytes [8]. Cellular FN is a mixture of FN isoforms. The alternative splicing of EIIIB and EIIIA and more complex splicing of the V or IIICS domain during transcription of cellular FN allows different isoforms of FN to be expressed in a tissue-dependent, temporally regulated, and cell-type-specific manner [9]. In humans, 20 potential FN isoforms can be generated [10]. Increased expression of the EIIIA+ and EIIIB+ isoforms of FN are associated with areas of physiological or pathological tissue remodelling, including wound healing and tissue repair. The most striking difference between these forms of the protein is their solubility. Plasma fibronectin is readily soluble in neutral Tris buffer at concentration of 1 to 2mg/ml. Cellular fibronectin on the other hand, is extremely insoluble, a factor which has impeded its characterization at the protein level.

***Structural Differences Among Fibronectins***

Many of the essential characteristics of plasma fibronectin are shared by all forms. Nevertheless, there seem to be measureable structural and functional differences, some of which are worthwhile considering here. Fibronectin appears in most instances to be dimeric, but unreduced fibroblast cell surface fibronectin preparations also exhibit species of very high molecular weight. These multimeric forms may indicate a higher degree of interchain disulfide bridging than is found in plasma forms and could account, at least in part, for the low solubility of the cell surface form in aqueous buffers at neutral pH. However, dimeric species present in cell surface preparations are still considerably less soluble than the dimeric molecules found in plasma fibronectin preparations. Furthermore, available evidence does not exclude the possibility that multimeric cell surface forms contain noncovalent interchain bonds that are resistant to dissociating agents such as urea, guanidine, and sodium dodecyl sulfate; precedent does exist for this type of interaction among proteins[11]

***Properties of Fibronectin***

It is a fast, B-globulin with a sedimentation coefficient of about 13 and a molecular mass, based on sedimentation equilibrium, of 440 kilodaltons (kd). Its frictional ratio is about 1.7. Cell culture fibronectin is 100- fold less soluble than plasma fibronectin in physiological saline. Soluble fibronectin is a disulfide-bonded dimer of 200 to 250kd subunits, as judged by polyacrylamide gel electrophoresis in sodium dodecyl sulfate with and without prior reduction. Reduced plasma fibronectin often migrates in these gels as 2 closely-spaced bands of equal intensity. Fibronectin secreted or shed by cultured cells migrates as a diffuse band, and differences in the ratio of labeled carbohydrate to labeled protein can be shown across the band in double label experiments. Fibronectin in amniotic fluid also appears to have a larger subunit than fibronectin in plasma.[12]

Insoluble fibronectin extracted from the cell layer of cultured cells is present as both disulfide-bonded dimers and multimers. Pulse labelling studies of cultured chick fibroblasts indicate that fibronectin is synthesized as a dimer and converts to a multimer with biphasic kinetics. Such studies suggest that the cysteines of the fibronectin dimer are oxidized in the cell layer and form disulfide bridges to adjacent fibronectin dimers and that formation of disulfide-bonded multimers contributes to the insolubility of cell layer fibronectin under physiological conditions.[13]

Disulfide-bonded multimers of fibronectin extracted from cell layers of normal cultured cells have the property of causing transformed cultured fibroblasts, which generally lack a fibronectin matrix, to assume more normal morphology, to have increased adhesion to the substratum, and to have less cell surface microvilli and membrane ruffles. To do these experiments, the fibronectin is solubilized in alkaline buffer

and neutralized just prior to being added to the transformed cells. The added fibronectin forms a matrix which, by immunofluorescence, is strikingly similar to that seen in non transformed cultures. Plasma fibronectin is less active than isolated cell layer fibronectin in restoring morphology, and reduction of cell layer fibronectin with dithiothreitol interferes with its ability to restore morphology. Thus, the disulfide-bonded fibronectin multimer has biological properties which are not shared by the fibronectin dimer.[14]

***Functions of Fibronectin***

The most thoroughly studied, and perhaps most basic, function of fibronectin is in the adhesion to solid substrates. Numerous studies have reported that fibronectin promotes the adhesion and/or spreading of cells on a variety of materials including plastic, collagen, gelatin and fibrin. Cells that synthesize their own fibronectin do not require exogenous fibronectin for adhesion and spreading, but many cells that produce little or none will respond to added fibronectin.[15] Among these cells are some oncogenically transformed cells that produce reduced quantities of fibronectin as a consequence of transformation.

Concomitant with the spreading induced by added fibronectin, cells often acquire highly ordered intracellular microfilament bundles .Furthermore, extracellular fibrils that contain fibronectin are often observed to correspond in their arrangement with intracellular microfilament bundles.These results, and others, suggest that there may be some form of physical connection between the extracellular matrix and the intracellular cytoskeleton. The molecular basis for this interaction is not understood as yet. However, the idea that the cytoskeleton and the extracellular matrix are part of a continuous supra-molecular assemblage has important implications for considerations of the effects of extracellular matrices on cellular behaviour.[16]

Interestingly, oncogenic transformation causes a pleiotropic change in cellular properties including reduced adhesion, rounded morphology, and loss of cytoskeletal organization, as well as loss of flbronectin. Because of these entire changes can, in some cases, be reverted by addition of fibronectin it is possible that they reflect a common effect of the transforming agent. Extensive studies have shown that loss of fibronectin is a common, though not universal, concomitant of transformation .The reasons for the loss appear to vary, and include reduced synthesis reduced binding and increased rates of degradation. Correlative studies suggest some association between loss of fibronectin and tumorigenicity in vivo but exceptions have been noted and preliminary studies suggest that a better correlation may exist between loss of flbronectin and acquisition of metastatic potential. Given the involvement of fibronectin in adhesion to extracellular matrices, effects on invasion and metastasis might be expected from alterations in this aspect of cellular function.[17]

During cancer progression, the extracellular matrix (ECM) of the tissue in which the tumour grows is extensively remodelled; both by degradation of pre-existing ECM molecules and by the neo-synthesis of ECM components, which in many cases are not present in the ECM of normal tissues.[18] Fibronectin (FN), a class of high-molecular-weight adhesive glycoprotein, plays a prominent role in mediating ECM function, because of its high abundance and its interaction with cellular components. Furthermore, the generation of tumour-associated FN isoforms allows the development of specific ligands (e.g., antibodies), which can be used for the selective delivery of therapeutic agents to the tumour environment. In view of these considerations, it is not surprising that FN is being used as a target for biomolecular intervention, both for the development of inhibitory molecules that block the interaction of FN with integrins and other receptors on the cell surface, and for the development of ligand-based targeted imaging and therapeutic strategies.[19] In this review, we briefly present the essential properties of FN, and we then focus on the therapeutic strategies that are currently in preclinical or clinical development and feature FN as a target, or that are based on FN fragments so as to promote tumour-growth inhibition. Fibronectin has been shown to play a central role in processes associated with tumour progression. In particular, α5β1 integrin and fibronectin have not only been shown to be up-regulated in tumours, but have also been reported to participate in tumour cell proliferation. Nam *et al* found that fibronectin and the extra domain (ED)-A splice variant of fibronectin were associated with higher α5β1-integrin expression in malignant as opposed to normal breast epithelial cells cultured atop Matrigel [20]. Interestingly, the authors also reported that total fibronectin, ED-A fibronectin and α5β1-integrin was markedly upregulated in the malignant breast cancer lines but not in non-malignant breast epithelial cells [21]. Similarly, Mierke *et al* also determined that α5β1 integrin was upregulated in MDA-MB-231 breast cancer cells and further demonstrated that fibronectin augmented the invasiveness of α5β1 expressing breast cancer cells cultured atop collagen hydrogels [22]. To investigate a mechanism responsible for α5β1-fibronectin in tumour growth, Mitra *et al* examined the activation of the receptor tyrosine kinase c-Met in human HeyA8 and SKOV3ip ovarian cancer cell lines following α5β1 engagement with fibronectin [23]. Results showed that binding of cellular α5β1 to fibronectin resulted in increased activation of the c-Met/FAK/Src signalling pathways in ovarian cancer cells [24]. Blocking ovarian cancer cell α5β1 interaction with fibronectin reduced c-Met mediated focal adhesion kinase (FAK) and Src phosphorylation in vitro and in vivo and additionally reduced tumour weight and proliferation in xenograft tumours [25], suggesting that α5β1-fibronectin interactions regulate cell signalling pathways important for ovarian cancer growth. While fibronectin appears to play a key role in multiple facets of tumour progression, it has also been shown to participate in processes associated with tumour migration, invasion and metastasis. To examine the role of fibronectin on tumour cell migration, Lou *et al* over expressed SOX2 to determine its role in ovarian tumour cell metastasis [26]. Here, the over expression of SOX2 upregulated fibronectin gene expression resulting in increased migration and invasion of the A2780 human ovarian cancer cell line in transwell chambers . Down regulation of fibronectin using siRNA resulted in a reversal of cell migration and invasion despite high expression of SOX2 indicating that SOX2 signals via fibronectin during tumour cell metastasis [27].

***Integrin-Fibronectin Interaction in Tumour Therapy Responses***

(A) Tumour cell α5β1 or β1 integrin interaction with fibronectin results in activation of cell signalling pathways which ultimately culminate in tumour cell resistance to chemotherapeutic agents. (B) Inhibition of α5β1 or β1 integrin interaction with fibronectin restores tumour cell sensitivity to chemotherapeutic agents resulting in increased cytotoxicity.

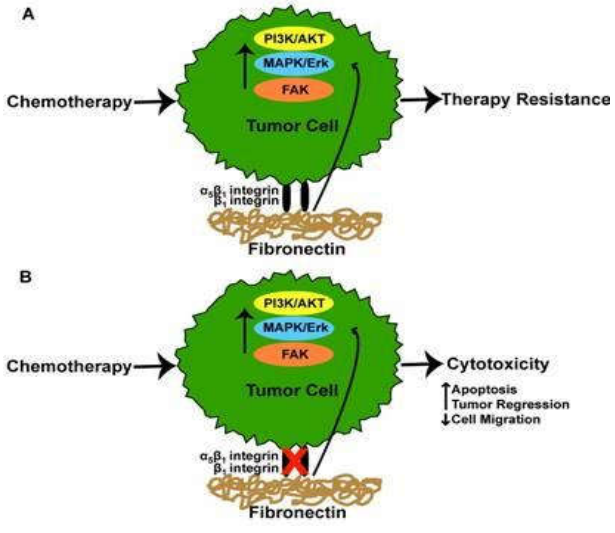


**Figure 2** (A), (B)

In vitro experiments have shown that fibronectin will promote cell migration in culture and can stimulate chemotaxis or haptotaxis. This raises the possibility that fibronectin might promote or guide cell migration in embryos and, indeed, fibronectin has been found in association with several areas of cell migration including avian gastrula, neural crest, area vasculosa, amphibian primordial germ cells and sea urchin primary mesenchyme. Perhaps also related to an involvement in cell migration is the stimulation by fibronectin of neurite outgrowth from retinal cell aggregates. It should be stressed that the presence of fibronectin in areas of cell migration does not prove that it is functionally involved, even less that it is the only relevant matrix component.

A functional role for fibronectin in phagocytosis was originally suggested on the basis of in vivo results that showed that levels of plasma fibronectin correlated with the ability of an organism to clear particulate debris, especially gelatin-coated particles from the circulation .It was suggested that fibronectin was acting as a "non-specific opsonin" for the reticuloendothelial system. This suggestion became even more interesting with the observation that fibronectin binds to certain bacteria. The recently reported binding of Clq by fibronectin [28] might also be important in phagocytosis of antibody aggregates or fragments of cells lysed by complement. In vitro studies have shown that fibronectin will indeed promote phagocytosis of gelatin-coated beads by certain macrophages although heparin is required as a cofactor.[29] No detailed studies have yet shown fibronectin to act as an opsonin for bacteria. Thus, the in vivo relevance of the "opsonic" activity of fibronectin remains unclear and is under active investigation. One interpretation of fibronectin-stimulated endocytosis is that it is simply a specialized form of cell spreading on a substratum with a small rather than an infinite radius of curvature.

Another possible role of plasma fibronectin is in haemostasis and thrombosis. During coagulation, fibronectin is cross linked to fibrin by factor XIIIa transglutaminase. Furthermore, platelets contain intracellular fibronectin, possibly in their agranules, and release it on activation.Activated platelets will also bind exogenous plasma fibronectin. Consequently, at the site of interaction of platelets with endothelial cell basement membrane, there are three possible sources of fibronectin; plasma, basement membrane, and the platelets themselves. Because other adhesive proteins such as von willebrands factor and thrombospondin are also present in the platelets, the basement membrane and the plasma, the adhesion of platelets is likely to be complex. The exact role of fibronectin in this process remains unclear but, under certain artificial in vitro conditions, fibronectin can promote the adhesion and/or spreading of platelets. Crosslinking experiments suggest that an interaction between fibronectin and thrombospondin occurs when platelets spread on solid substrata. Thrombospondin has also been implicated in platelet aggregation. Thrombospondin is a high-molecular-mass glycoprotein that is synthesized and secreted by vascular endothelium and certain other cell types in culture [30]. It is also a major protein of the human platelet, which can be secreted following stimulation by thrombin or collagen [31]. After platelet activation, thrombospondin is found both in a soluble form and bound to the platelet membrane [32]. Its binding to the platelet membrane is Ca2+ dependent. [33]

Finally, fibronectin has been implicated in the regulation of several differentiation pathways. Fibronectin has been reported both to stimulate myogenesis and to inhibit myoblast fusion and to inhibit chondrogenesis. [34] The precursor cells of both the myogenic and chondrogenic lineage are fibronectin-positive, and there appears to be a loss of fibronectin during progression along these two differentiation pathways. Fibronectin has also been reported to inhibit melanogenesis and to promote adrenergic differentiation in explanted neural crest cells. Extracellular matrices have long been thought to play important roles in development. Fibronectin has now joined collagens and proteoglycans as a candidate for a role in these processes, as have even more recently discovered glycoproteins such as laminin and chondronectin. [35] Clearly the role of the various matrix constituents, singly and in combination, in various differentiative events will be an active area of research in the next few years. Fibronectins therefore appear to be involved in an almost embarrassingly large array of cellular functions.

***Functional Differences Among Fibronectins***

Fibronectins are major participants in a variety of cellular activities such as substrate adhesion and cell spreading, alignment, and morphology. These adhesive functions are brought about, or at least partially modulated by, the binding affinity of fibronectin for certain extracellular macromolecules such as collagen, fibrin(ogen), and glycosaminoglycans (e.g., heparin). Certain recent studies, have compared the capacity of the fibroblast cell surface and plasma forms to mediate certain

of these functions and suggest that some significant differences exist. Either cellular or plasma fibronectin can effectively mediate attachment of cells to collagen and either is equally effective in promoting spreading of baby hamster kidney cells on plastic substrates.[36] However, Collagen was reportedly only about half as effective as cell surface fibronectin in promoting attachment of a transformed hamster cell line to a plastic dish (NIL8-HSV).[37] Yamada and Kennedy[38] found that plasma fibronectin was 50 times less active than fibroblast fibronectin in restoring morphology and alignment to a transformed fibroblast cell line and 150 times less active in agglutinating formalin-fixed sheep erythrocytes. An explanation for these differences is not yet at hand, but could be related to the presence or absence of multimeric forms.

## CONCLUSION

Analysis of the structure of fibronectins reveals a modular structure that appears well suited for functioning as an adhesive ligand-like molecule. The suggested roles of fibronectins in complex biological phenomena such as cell migration, cellular differentiation, haemostasis and thrombosis, reticuloendothelial clearance, and cancer all require much more extensive investigation. Studies of these phenomena in vivo will be contingent upon progress on the biochemical, immunological, and cell biological analyses of fibronectins. Several other proteins of a type similar to fibronectins also function as cell-matrix ligands (eg, laminin, chondronectin, von willebrands factor, thrombospondin) and this list is likely to grow rapidly.

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