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Fibronectin in cell adhesion and invasion

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Summary

Fibronectin plays a major role in the adhesion of many cell types. The extent of cell adhesion in vitro is related not only to the ability of the cells to interact with matrix-bound fibronectin, when it is present, but also to the synthesis or lack of synthesis of fibronectin by the cells, and to the lack of deposition of synthesized fibronectin into an insoluble matrix surrounding the cells. Many malignant cells, regardless of whether they synthesize subnormal or normal amounts of fibronectin, fail to deposit that fibronectin into a surrounding insoluble matrix. The lack of fibronectin around such cells appears to reflect a general absence of extracellular matrix since other matrix components, such as collagen, laminin, and heparan sulfate proteoglycan, are concomitantly missing. Cells that lack their own cell surface fibronectin due either to lack of deposition or to lack of synthesis can nevertheless adhere to insoluble fibronectin matrices elaborated by other cells. These cellular characteristics appear to be associated with cell migration in vivo during embryogenesis, and the same characteristics may enhance the invasive potential of malignant cells. The remarkable effects that fibronectin has on cellular adhesion and the association of lack of extracellular matrix components with poorly differentiated and highly metastatic tumors in vivo mandates that more be learned about the molecular and cellular details of the interactions of cells with their surrounding matrix. Important information concerning tumor invasion will parallel such an understanding and may eventually become the basis for therapeutic approaches.

Introduction

Significant progress has recently been made in the understanding of the composition and functions of extracellular matrices. These structures are mainly composed of three types of macromolecules: collagens, proteoglycans and glycoproteins (1). Collagens exists as a group of genetically distinct but related molecules with different tissue localizations (2, 3). Similarly, proteoglycans are a highly polymorphic group of molecules with specialized distributions in tissues and different types of extracellular matrices (4). Fibronectin (5) and laminin (6) have been identified as major glycoproteins of

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connective tissue and basement membranes, respectively. These three classes of molecules interact with one another forming the insoluble supramolecular complexes that constitute extracellular matrices.

The thought that cells communicate with the extracellular matrix that surrounds them and that this interaction influences cellular differentiation and migration (7) has become widely accepted. These cell-matrix interactions also appear to be important for tumor invasion and metastasis. A characteristic common to many extracellular matrix molecules is their ability to interact with cells, making the matrix adhesive to cells. Malignant cells often fail for one reason or another to possess an extracellular matrix. This fact and the observation that decreased adhesiveness is one of the most consistent characteristics of malignant cells has led to an intensive study of extracellular matrices as determinants of the invasive behavior of tumor cells. Fibronectin has emerged as a prototype adhesive extracellular matrix glycoprotein. The purpose of this chapter is to discuss the current understanding of the role of fibronectin in affecting neoplastic growth and tumor behavior.

Structure-function relationships of fibronectin

Fibronectin is a multifunctional protein

Fibronectin exists in two forms: either as an insoluble protein in tissues and in the extracellular matrix of cultured cells or as a soluble protein in plasma, in other body fluids and in the media of cultured cells. The structural and functional properties of soluble and insoluble fibronectin are very similar, and the two forms appear to be interchangeable in some respects. Plasma fibronectin can become incorporated into extracellular matrices of cultured cells (8) and into tissues in vivo (9), and a large part of the fibronectin produced by cultured cells remains soluble in the cultured media in vitro.

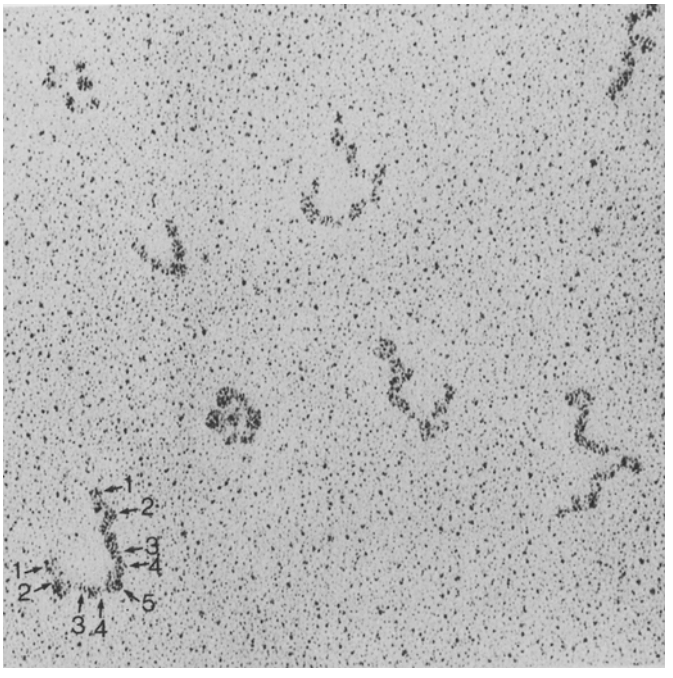
Fibronectin interacts with many other macromolecules, including collagens, glycosaminoglycans (and proteoglycans), fibrinogen and fibrin, some bacteria, and a structure of an unknown nature at the cell surface of most eukaryotic cells. Based on recent structural studies carried out in a number of laboratories, we are beginning to discern the molecular arrangements which underlie the multitude of biological activities in fibronectin and their significance to the functions of the molecule (for recent reviews see 5, 10, 11).

The various binding activities of the fibronectin molecule reside in structurally independent, apparently globular domains along the elongated fibronectin polypeptide chain which has a molecular weight of about 220,000. Two such chains linked together by disulfide bonds at the COOH-terminus make up the dimeric fibronectin molecule. Figure 1 illustrates the shape of fibronectin as viewed by electron microscopy after rotary shadowing.

Each of its binding activities appears to play a role in the biological behavior of fibronectin. The collagen- and proteoglycan-binding activities are likely to be involved in anchoring fibronectin to extracellular matrix. Glycosaminoglycans and proteoglycans enhance the interaction of fibronectin with collagen (see ref. 5). Such interactions among several matrix components may be important for the organization of extracellular matrices. Intermolecular crosslinking by disulfide bonding through the free sulfhydryl group(s) of the molecule also appears to be important in the insolubilization of fibronectin (12, 13). The interactions of fibronectin with other matrix components or with fibrin in a wound leave the cell attachment site of fibronectin available for binding of cells to the matrix. It is through this cell-binding activity that fibronectin is likely to exert its most significant biological effects.

Insoluble fibronectin promotes cell attachment

The interaction of cells with fibronectin is manifested through the attachment and spreading of the cells (Figure 2; 14–16). For this activity to be demonstrable, the fibronectin must be insolubilized on a surface or in a matrix; little interaction occurs between cells and soluble fibronectin (17). The reasons for this are not entirely clear, but it appears that the affinity of the interaction of a single fibronectin molecule with the cell surface is



1. Fibrin-binding
2. Collagen-binding
3. Cell attachment
4. Glycosaminoglycan-binding
5. Interchain disulfide bond

Figure 1. Appearance of fibronectin under the electron microscope after rotary shadowing. A field showing several individual molecules is shown. Some of the structural features known from biochemical work are indicated in one of the molecules.

low and that cooperative binding of many fibronectin molecules on a solid surface is required for a productive interaction to take place.

Much of the current work on fibronectin is directed at understanding the molecular aspects of the interaction between fibronectin and the cell surface. The cell-binding domain, which is in the middle portion of the molecule, has been isolated as an 11 kilodalton fragment, and its complete primary structure has been determined (18). Quite recently, we have shown that synthetic peptides modeled after portions of this sequence can have cell attachment-promoting activity (19). These peptides now provide an excellent tool for analysis of the identification of the cell surface structure that recognizes fibronectin. As discussed below, the fibronectin-cell interaction may be perturbed in some malignant cells and an understanding of its molecular basis could, therefore, be of great importance.

Fibronectin in nontumorigenic and tumorigenic cells

In considering the effects of extracellular matrix on cells, it is important to note that there are three essentially independent aspects of the interaction of a given cell with extracellular matrix: 1) the production of extracellular matrix proteins by the cell, 2) the deposition of the proteins produced into an insoluble matrix, and 3) the ability of the cells to interact with this matrix and with matrices made by other cells. Normal cells typically produce matrix components, lay them down into a matrix, and then interact with this matrix. A defect in any one of these processes could result in abnormal adhesion (Figure 3).

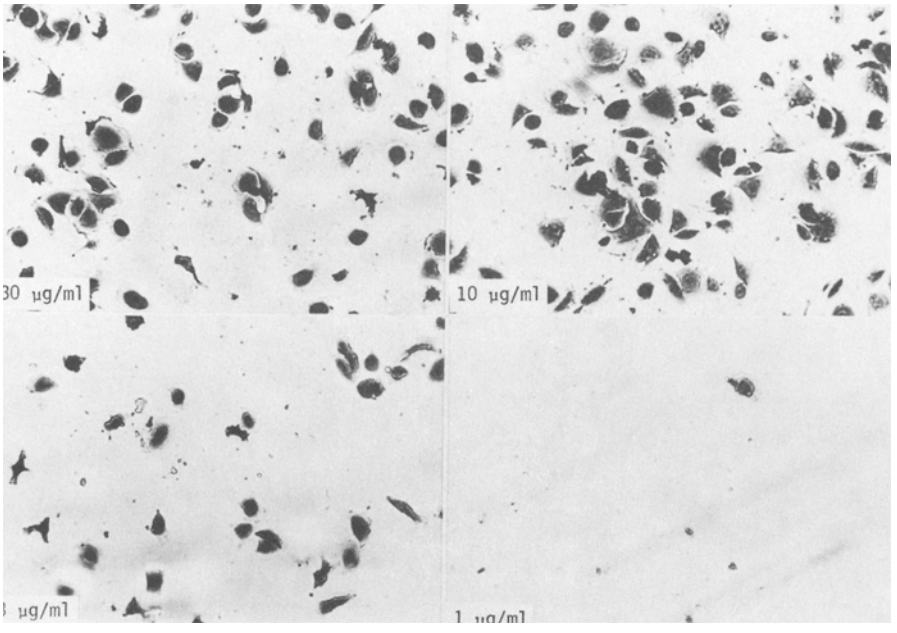


Figure 2. Attachment and spreading of cells on a surface coated with fibronectin. Plastic microtiter wells were coated with (A) 30, (B) 10, (C) 3 and (D) 1 μg/ml of fibronectin, and normal rat kidney cells were added into the wells. After 1 h, unattached cells were removed by washing and the remaining cells were fixed and stained. The attached cells in wells A and B represent about 80% of the cells added to the well.

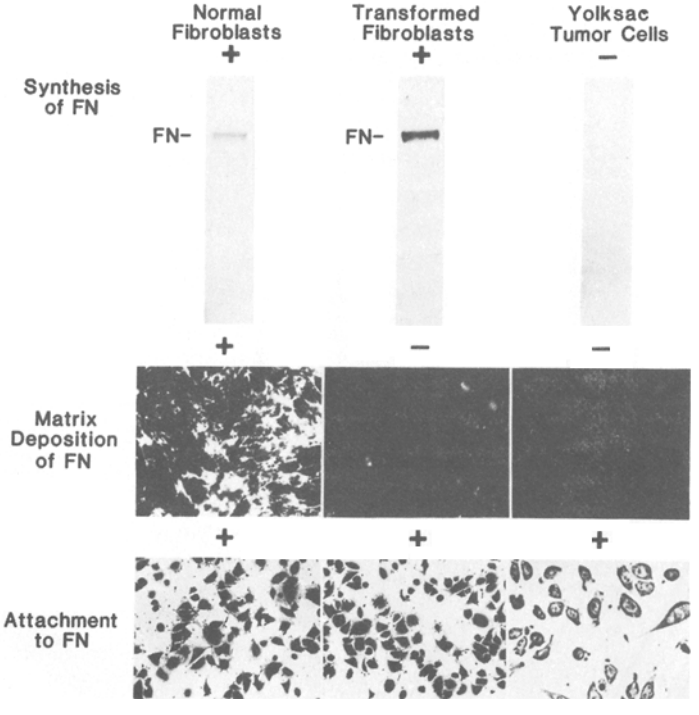


Figure 3. Illustration of the three different aspects of cell-matrix interaction. Normal cells (left column) typically produce fibronectin which can be isolated from their culture media or from the cell layer and analyzed by sodium dodecyl sulfate/polyacrylamide gel electrophoresis (upper panel). Normal cells also deposit this fibronectin into a matrix where it can be visualized by immunofluorescence (middle panel) and the cells are able to attach to a surface coated with fibronectin (bottom panel). The two malignant cell lines (middle and right columns) shown in this illustration differ from normal cells with respect to the fibronectin system.

Malignant cells produce fibronectin, but often do not deposit it in a matrix

Malignantly transformed cells retain the capacity to produce fibronectin if their cell of origin had it, but usually fail to deposit fibronectin into a matrix. That the lack of matrix deposition correlates with the transformed state is clearly shown by the restoration of fibronectin deposition upon reversal of the transformation (20–24).

The lack of matrix fibronectin in malignant cells seems to reflect a generalized absence of extracellular matrix in such cells. Transformed rat and mouse cells lack cell surface fibronectin, laminin, and heparan sulfate proteoglycan which are all present in their normal counterpart cells codistributed in the same cell surface structures. (Figure 4; 25–27). Collagen also codistributes with fibronectin and is lost upon transformation (28–30). The codistribution of these macromolecules in the matrix is not surprising because they all have been shown to interact with at least one other matrix component (see ref. 5).

Tumor cells in vivo, at least in some cases, also express reduced amounts of matrix fibronectin (31, 32). In addition, a generalized lack of matrix components similar to that observed in vitro is manifested in the absence of basement membranes normally detectable by immunohistochemical staining for laminin and type IV collagen (33–35). A strong correlation exists between the presence of residual basement membranes and the degree of morphological differentiation of a tumor, tumors with the lowest degree of differentiation having no detectable basement membranes. Whether the lack of fibronectin and other matrix components is due to lack of deposition or abnormal destruction is subject to speculation. The cell culture studies discussed above point to a defect in deposition, but proteases with various degrees of specificity toward the extracellular matrix and basement membrane components have also been implicated (36–39).

The correlation between lack of cell surface fibronectin and tumorigenicity does not appear to be straightforward. Malignant cell lines that retain a fibronectin matrix are not uncommon (40–43), and cells that do not lay down a matrix in vitro can acquire cell surface-associated fibronectin when they grow as a tumor in vivo (44–46). In this latter case, however, it seems that the lack of fibronectin matrix demonstrable in vitro reflects an abnormality of cell adhesion mechanisms that is likely to manifest itself in some form also in vivo. Furthermore, it has been found that when cells positive for matrix fibronectin are obtained from tumors, cells isolated from primary tumors have more fibronectin in vitro than cells isolated from metastases (42, 47). It appears that a sliding scale exists regarding the expression of matrix fibronectin in various malignant cells. Given the striking effects of fibronectin on cell adhesion, it is likely that in those cells

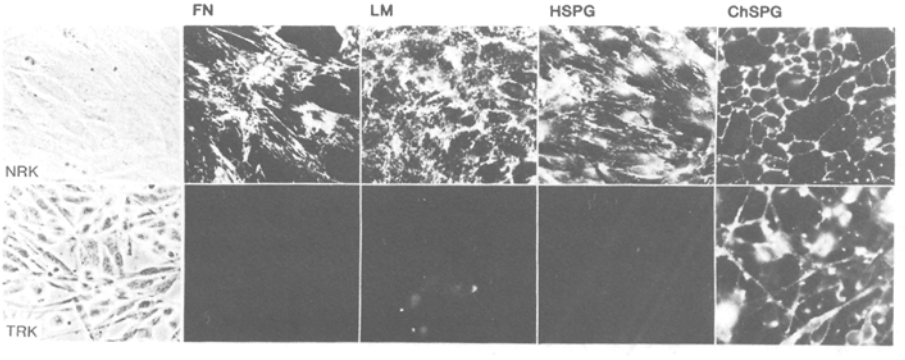


Figure 4. Lack of normal extracellular matrix in transformed rat kidney cells (TRK) as revealed by lack of immunofluorescent staining for fibronectin (FN), laminin (LM) and heparan sulfate proteoglycan (HSPG) present in normal rat kidney cells (NRK). The transformed cells do retain chondroitin sulfate proteoglycan (ChSPG) at their surface.

which lack it, its absence influences the metastatic capacity of cells.

The reasons for the lack of fibronectin deposition are not known, but one possible reason could be an abnormality of the fibronectin. However, fibronectin from transformed cells can be indistinguishable from normal fibronectin. Extensive characterization of fibronectin from two transformed cell lines has shown that these fibronectins are structurally and functionally intact (48, 49). Furthermore, protein and DNA sequencing have shown that the cell attachment domain of fibronectin in a human fibrosarcoma cell line is identical to that of plasma fibronectin (18, 50) and, therefore, not likely to be functionally defective.

It is quite possible that abnormal fibronectins will be found as a larger number of malignant cell lines is examined in this regard. Our recent results show that a change in the fibronectin gene as small as a point mutation may be enough to render it inactive in cell attachment. Using synthetic peptides we have shown that the cell attachment recognition site in fibronectin is only a few amino acids long and that single amino acid changes in the active peptides will render them inactive (19; Pierschbacher and Ruoslahti, submitted). Moreover, the active site in fibronectin contains a serine residue which could be susceptible to phosphorylation (Pierschbacher and Ruoslahti, submitted). Since a difference has been found in the degree of phosphorylation of fibronectin from normal and transformed cells (51), it will be important to determine whether phosphorylation might inactivate the cell attachment site.

Tumor cells have a receptor for fibronectin and they interact with fibronectin-coated surfaces

A given cell may or may not be capable of interacting with fibronectin. This interaction appears to depend on the presence at the cell surface of a structure that recognizes the cell attachment site of fibronectin. This cell surface structure is often referred to as a 'receptor' and this term will be used here for convenience even though it is not known whether this recognition structure has the characteristics of a classical receptor. Malignantly transformed cells recognize fibronectin (48, 52–54), indicating the presence of a receptor for fibronectin in these cells. However, there may be a relationship between the quantity or activity of the cell surface receptor and the ability of the cell to deposit fibronectin into an insoluble matrix since some cell lines defective in fibronectin deposition also have been found to interact less well with fibronectin than their normal counterparts (49, 55). Future studies which identify the receptor and develop methods that will allow its quantitation in normal and transformed cells will be of great interest.

Corollaries of the transformed fibronectin phenotype

Cells lacking matrix fibronectin migrate in vivo

It has been difficult to find definite correlations between the fibronectin system and tumor invasion. This is likely due to the heterogeneity of the malignant phenotype; in some tumor cells the lack of fibronectin deposition may be a significant part of the phenotype, in others it may not be necessary for the cells to be capable of invading surrounding tissue. A more convincing case for the influence of fibronectin on cell migration has been made in experiments conducted with embryos.

In the embryo, neural crest cells migrate ventrally from their origin to give rise to sensory and sympathetic neurons, glial cells, and chromaffin cells in the gut area. Various types of cells can be injected into the embryo and their migration along the migration pathway observed. Using this system, it has been found that the ability of cells to become translocated along the neural crest pathway correlates with the lack of cell surface fibronectin (56). A particularly interesting set of observations has been made in the same test system using protein-coated latex beads as probes (57). When beads coated with albumin and fibronectin were injected into the pathway, the albumin-coated beads (as well as beads left uncoated) migrated along the pathway, but beads coated with fibronectin failed to do so. These results strongly suggest

that the presence or absence of fibronectin deposited around a given cell can determine whether that cell participates in migratory movements during development. The phenotype of the migrating cell appears to be that of lacking cell surface fibronectin in vitro.

Attachment of tumor cells to fibronectin and other matrices may also be important in migration and invasion

As discussed above, malignant cells that lack their own fibronectin matrix may be at an advantage when it comes to migration in tissues. On the other hand, it may be important for migrating and invading cells to be able to interact with fibronectin matrices made by other cells. To give rise to blood-borne metastases, tumor cells must adhere to the capillary endothelium and penetrate the capillary walls into the surrounding tissue. Metastatic cells have been found to have a particular affinity for the extracellular matrix of endothelial cells in vitro (58, 59). Fibronectin seems to play a role in such adhesion since antibodies to fibronectin can partly prevent this adhesion (39). Contact with a fibronectin-coated surface has been shown to enhance the migration of normal (60) and malignant (61) cells in vitro. Taken together, this information suggests that the spread of tumor cells through tissues – including extravasation – requires attachment to extracellular matrices encountered along the migration pathway. To move on, a cell must subsequently be able to detach from these matrices.

An ability to detach may be a particular characteristic of invasive cells. Tumor cells are well equipped to degrade matrices (39) and this is likely to be one of the mechanisms for detachment. We have recently provided evidence for another possible mechanism (62). Transformed fibroblastic cells express chondroitin sulfate proteoglycan at the cell surface, in spite of the fact that they lack matrix components such as fibronectin, laminin, and heparan sulfate proteoglycan (Figure 4; 25). This observation and the finding that chondroitin sulfate is increased in certain neoplasms (63) led us to investigate the effect of a chondroitin sulfate proteoglycan isolated from yolk sac tumor cells (64) on the adhesion of these tumor cells to extracellular matrices.

We found that the proteoglycan inhibited the adhesion of the tumor cells to substrata containing fibronectin or type I collagen (62). Interestingly, the effect of the proteoglycan was selective in that it depended on the ability of the adhesive substratum to bind the proteoglycan. The proteoglycan did not inhibit the attachment of the cells to type IV collagen, which bound much less proteoglycan than did type I collagen. Similarly, attachment of the cells to fibronectin fragments which did not bind the proteoglycan was not affected. Based on the selectivity of effects of the tumor proteoglycan on the adhesion of cells to extracellular matrices, we have suggested that such proteoglycans may promote tumor invasion by reducing interaction of cells with interstitial extracellular matrices while permitting attachment to basement membranes.

Conclusion

One of the most consistent in vitro characteristics of malignant cells is their reduced adhesiveness. Much of the reduced adhesiveness of tumor cells appears to be due to their failure to deposit fibronectin and other proteins into an extracellular matrix. There is reason to believe, then, but by no means has it been proven, that the lack of matrix surrounding the cells would promote the migration of tumor cells in tissue and that this would result in invasion. As the molecular basis for assembly of extracellular matrices and their interaction with cells is being worked out, a better understanding of the invasion process is likely to ensue.

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