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Cell Surface Fibronectin and Oncogenic Transformation

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Fibronectin is a large glycoprotein at the cell surface of many different cell types; a related protein is present in plasma. Fibronectin is a dimer of 230,000-dalton subunits and also occurs in larger aggregates; it forms fibrillar networks at the cell surface, between cells and substrata and between adjacent cells, and it is not a typical membrane protein. Cell surface fibronectin is reduced in amount or absent on transformed cells and in many cases its loss correlates with acquisition of tumorigenicity and, in particular, metastatic ability. Exceptions to the correlations with transformation and tumorigenicity exist. Loss of fibronectin and the resulting reduced adhesion appear to be involved in pleiotropic alterations in cell behavior and may be responsible for several aspects of the transformed phenotype in vitro. Fibronectin interacts with other macromolecules (collagen/gelatin, fibrin/fibrinogen, proteoglycans) and is apparently connected to microfilaments inside the cell.

Key words: fibronectin structure and properties, cytoskeleton, cell surface proteins, fibronectin distribution, fibronectin interactions, transformation

Since the initial report in 1973 that a large protein was lost from the surfaces of virally transformed cells [1], there has been a large amount of work that has by and large confirmed the generality of this observation. This surface protein is now generally known as fibronectin. Some of the probable implications of the loss of fibronectin for the transformed phenotype in vitro are becoming clear, and several analyses have attempted to clarify possible relationships with the malignant phenotype in vivo. In this article, we shall briefly review the current state of this area of research. No attempt will be made to be exhaustive, but we will rather summarize the main points that are established and attempt to identify the outstanding questions that require further research. Several detailed reviews of the subject have been published and these may be consulted for more complete bibliographies [2–4].

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DISTRIBUTION OF FIBRONECTINS

Although cell surface fibronectin was first described in fibroblasts, it has subsequently been detected on many other cell types in culture (Table I). Analysis of tissue sections by immunofluorescence or immunoelectron microscopy has also identified cross-reacting material in many locations in vivo [22–24]. The discovery [33] that cell surface fibronectin – variously known as LETS protein, CSP, SF-antigen, galactoprotein a or Z – is immunologically related to a plasma and serum protein known as cold-insoluble globulin (CIg), leads to recognition of an even wider distribution of proteins of this type. These proteins are known collectively as fibronectins. Although they are cross-reactive immunologically, exact identity has not been shown. In fact, it seems clear that the cell surface form identified on cultured cells, which is rather insoluble [34, 35], differs somewhat from the soluble plasma form. The cellular source of the plasma form has not been identified. The possibility of cell type-specific differences among fibronectins has not been studied in any detail, and there has been little biochemical analysis of the antigenically related material detected in tissue sections.

The major in vivo locations of fibronectins are in soft connective tissue stroma, associated with basement membranes, and in body fluids such as plasma and cerebrospinal and amniotic fluids (Table I). In tissue culture, fibronectin has been most extensively studied on fibroblasts, of which it is a major surface protein, consistent with the connective tissue location in vivo. Other major producers in culture are myoblasts, endothelial cells, and amniotic cells (Table I), and several other cell types have been reported to produce fibronectin, usually at lower levels [15–21]. Some apparent discrepancies exist between the in vivo and in vitro distributions. Neural tissues, both neuronal and glial, appear to lack fibronectin in vivo, but some glial cells have been reported to make it in vitro. Similarly, cartilage in vivo is free of fibronectin [31], and while differentiated chondrocytes in culture also lack fibronectin, predifferentiated or dedifferentiated chondrocytes do synthesize it [31, 32]. Hormonal regulation of fibronectin production has been demonstrated [36, 37] and cells regulate their levels in response to growth conditions [38, 39]. Clearly, therefore, the levels produced by a given cell type can be modulated.

STRUCTURE OF FIBRONECTIN

Fibronectins, both cell surface and plasma forms, are large glycoproteins with subunit molecular weights of 230,000 ± 20,000, and are about 5–7% carbohydrate. Most or all the carbohydrate side chains appear to be of the complex asparagine-linked type [40, 41]. The carbohydrate contents of fibronectin chains appear to vary [14, 42]. Fibronectins are in fact dimers of the basic subunits held together by disulfide bonds [26, 27, 34, 35, 42–44]. The interchain disulfide bonds are located very close to one end [42, 45], probably the C terminal [46, 47]. On the cell surface, but not in plasma, fibronectin also occurs as high-molecular-weight aggregates whose integrity depends on disulfide bonds [43, 44]. Disulfide-bonded aggregates could arise through reaction of the single free sulfhydryl group present on each subunit of fibronectin [42]. Within fibronectin, there appear to be globular domains joined by flexible regions, as determined by physical methods [48, 49]. Different domains can be separated by partial proteolytic digestion [42]. These separable fragments differ in composition. There is a small (25,000–30,000 daltons), highly disulfide-bonded but carbohydrate-free region and a larger (200,000 daltons) fragment that is relatively poor in cystine, but contains most of the carbohydrate and the free sulfhydryl [42]. The 200,000-dalton fragment can be further fragmented to yield a fragment of

30,000–40,000 daltons that contains the site by which fibronectin binds to gelatin [50–52] and a different fragment, which binds to heparin [53, 54], is also probably located in the 200,000-dalton region.

PROPERTIES OF CELL SURFACE FIBRONECTIN

Cell surface fibronectin is arranged in fibrillar arrays that can be detected by immunofluorescence or immunoelectron microscopy (Fig. 1). The pattern of the fibrils varies for different cells and, for a given cell type, depends on culture conditions, especially cell density. Isolated cells have fibronectin predominantly beneath them, between the cell and the substratum [39]. Cells in contact often have fibronectin between them, and dense cultures have elaborate fibrillar networks around and above the cells (Fig. 1). Fibronectin is most prevalent in dense or growth-arrested cultures; growing cells have less, and mitotic cells have very little [38, 39].

Cell surface fibronectin is relatively immobile and does not readily form patches and caps, as do certain integral membrane proteins [39, 55, 56]. The fibrils can be left behind on the substratum when cells are detached [39] and although some crude plasma membrane preparations contain fibronectin, it is possible to separate fibronectin from plasma membrane vesicles and it can be isolated in a nonmembranous cell surface fraction probably corresponding with the cell surface coat [57, 58].

All of these results suggest that fibronectin is not a typical membrane protein but should be considered rather as a constituent of the surface coat, glycocalyx, or extracellular matrix. Consistent with this idea is the difficulty of solubilizing fibronectin from cell surfaces. This cannot be accomplished by nonionic detergents, high- or low-salt, or chelating agents, but requires chaotropic reagents [34]. Release from cell surfaces is also promoted by reducing agents, a phenomenon that is consistent with the extensive disulfide bonding [43]. The fibrillar matrix of fibronectin is readily removed by proteolytic enzymes.

TABLE I. Distribution of Fibronectins

	Representative references
In vitro – Cell surface and secreted	
Fibroblasts – primary cultures and established lines	1, 2, 5–8
Myoblasts – primary cultures and established lines	9, 10
Endothelial cells	11–13
Amniotic cells	14
Some glial cells	15
Some epithelial cells	16–18
Teratocarcinoma embryoid bodies	19–21
In vivo	
Basement membranes	22–24
Soft connective tissue stroma	22–24
Plasma 300 μg/ml (serum has less)	25–27
Amniotic fluid	14, 28
Cerebrospinal fluid	29
Absent from:	
Preimplantation embryos (mouse)	20, 24
Neural tissue (neuronal and glial)	30
Cartilage and differentiated chondrocytes	31, 32

FIBRONECTIN AND TRANSFORMATION

In most cases, transformation of cells by DNA or RNA tumor viruses leads to loss of fibronectin from the cell surface, although some exceptions do occur. If the viruses are temperature-sensitive for transformation, then the loss of fibronectin is temperature-sensitive. Chemical and spontaneous transformants have been less extensively studied, but in many cases they also showed reduced levels of cell surface fibronectin. Transformants of fibroblasts, myoblasts [9], glial cells [15], and epithelial cells [16] have all been reported to lose fibronectin. Thus, there is a good, albeit not universal, correlation between loss of fibronectin and in vitro transformation of several cell types by a variety of transforming agents (see reviews in references 2–4).

The exact degree of parallelism between in vitro transformation and tumorigenicity and malignancy in vivo remains uncertain. Several studies have investigated the relationship between loss of fibronectin and in vivo aspects of the tumor phenotype. In a series of adenovirus-transformed rat cells, there was a good correlation with tumorigenicity [59]. In other series of cells, the correlation was less good [60, 61]. In these studies, the correlation was between in vitro expression of fibronectin and hyperplasia in vivo. More recent studies using immunofluorescence analysis of tumor sections have shown a much better correlation between in vivo expression of fibronectin and tumorigenicity [62]. It appears that some transformed cells that do not express fibronectin in vivo can turn on expression in vitro. This is reminiscent of the behavior of some normal cells discussed earlier. In any event, it now seems likely that some of the lack of correlation between in vitro expression of fibronectin and in vivo tumorigenicity may arise from cells that are in vitro false-positive for fibronectin. Also several studies have suggested that the best correlation is between loss of fibronectin and acquisition of metastatic capability, rather than with hyperplasia [62–64]. It remains to be seen how well these correlations will stand up to further experimental tests but, at present, the correlations are good enough to suggest that fibronectin plays a significant role in some aspect(s) of in vitro transformation and in vivo malignancy.

In order to investigate directly its role in the determination of various parameters of the transformed phenotype in vitro, purified fibronectin has been added to cultures of transformed cells. This causes increased adhesion, flattening, and elongation of cells and the cells align with each other in patterns characteristic of normal cells [65, 66]. The cells show reduced numbers of microvilli and surface ruffles [67] and show increased organization of microfilaments into bundles [66, 68]. In contrast with these effects on adhesion and morphology, fibronectin has no effect on growth in monolayers [65] or in agar (I. U. Ali, unpublished data) nor on cyclic AMP levels[65] or the rates of nutrient transport [66, 69].

The simplest interpretation of the pleiotropic effects of fibronectin on transformed cells is that the primary effect is to increase adhesion to the substratum and that the other properties follow from this. This is outlined in Figure 2. Thus, increased adhesion would lead to cell flattening on the substratum; this would lead in turn to reduction in surface microvilli and ruffles, since the surface membrane in these structures would be utilized in the increase in overall surface area associated with spreading. Several workers have proposed that contact inhibition of movement [70, 71] can best be explained as a reflection of inhibition of underlapping consequent upon effective cell-substratum adhesion [72–74]. Increasing the adhesion by adding fibronectin would therefore be expected to lead to reduced underlapping and thus to contact inhibition of movement and alignment of the cells. It has been argued that the effects of fibronectin on microfilament organization can also be ascribed merely to adhesion [68]. However, other explanations are also possible

[66] and, in light of recent results to be discussed later, it appears that the effects of fibronectin on the cytoskeleton are more complex and also involve direct interactions (see next section).

Thus, a plausible hypothesis is that the pleiotropic effects of fibronectin on the behavior of cells arise from an increase in cell-substratum adhesion. The corollary of this hypothesis is that reduction of fibronectin levels by transformation could lead to reduced cell-substratum adhesion and consequently to alterations in the parameters discussed above, all of which alterations are characteristics of the transformed phenotype.

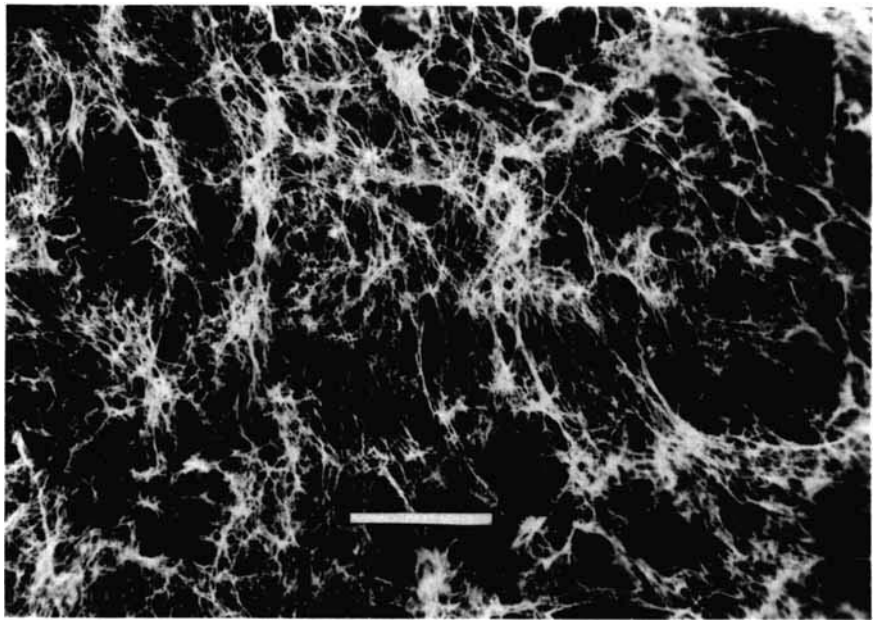

Fig. 1. Fibrillar network of fibronectin on confluent culture of NIL.8 hamster fibroblastic cells. Cells were grown to confluence, fixed, and stained with antibody to fibronectin. Magnification: bar represents 50 μ.

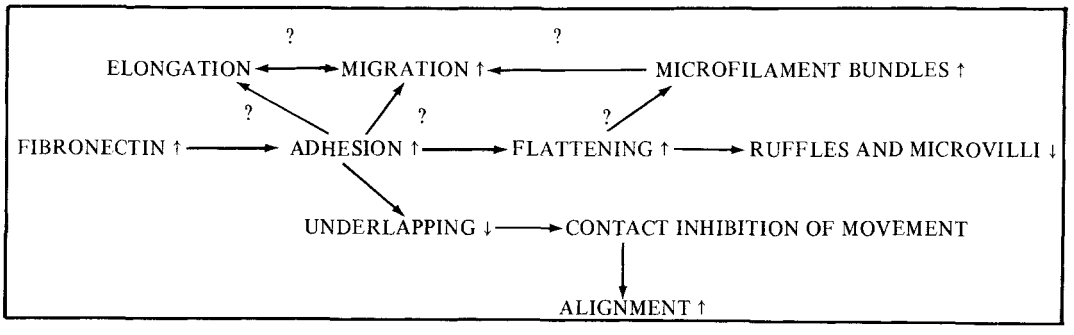

Fig. 2. Diagrammatic representation of the effects of fibronectin on transformed cells. Fibronectin has been shown to produce all of the effects shown: The diagram predicts likely interrelationships among the effects. Hence, increased adhesion is thought to lead to cell flattening and thus to reduced numbers of ruffles and microvilli. Question marks indicate questionable interrelationships such as a simple induction of microfilament bundles by cell flattening (see text) or the possible relationships among adhesion, migration, and cell elongation, which are not clearly understood.

The reasons for the reduced levels of fibronectin that occur on transformation remain incompletely understood. Reduced rates of biosynthesis provide a partial explanation [75, 76] but increased turnover [5, 8, 75] and decreased ability to bind fibronectin [47, 77] also contribute. The possibility that transformation-induced proteolytic enzymes, in particular plasminogen activator, might be responsible for removal of fibronectin has been examined. It is clear that plasminogen is not required [78–80] and that extensive cleavage of fibronectin into the characteristic proteolytic fragments discussed earlier does not occur [80]. However, subtle cleavage of fibronectin or cleavage of a molecule necessary for its binding to cells by proteolytic enzymes not requiring plasminogen remain possibilities.

FIBRONECTIN AND THE CYTOSKELETON

Since alterations in fibronectin and alterations in the organization of the cytoskeleton, in particular of microfilament bundles, both occur on transformation, it seemed possible that the two might be related. This idea was strengthened by the effects of fibronectin readdition on the arrangement of microfilament bundles [66, 68] and by the observation that cytochalasin B, a drug that disassembles cytoplasmic microfilaments, leads to release of fibronectin from the cell surface [39, 81]. Double-label immunofluorescence analyses showed that there was definite correspondence between the fibrillar arrays of fibronectin and actin in cells under a variety of conditions [82] (Fig. 3), and recent electron microscopic analysis has confirmed this [83]. These results suggest a transmembrane connection between fibronectin and microfilaments. Analogous investigations have failed to detect any relationship between fibronectin and microtubules or intermediate filaments [39, 81, 82].

Hence, it appears that the influence of exogenously added fibronectin on microfilaments is likely to be more direct than a simple effect on cell spreading. The patterns of fibronectin are consistent with an involvement in adhesion plaques at the base of the cell. These plaques are sites of attachment of microfilament bundles to the plasma membrane [84, 85].

Since neither actin nor fibronectin appears to be an integral membrane protein, there must be intervening proteins connecting the two. It is therefore of some interest to investigate the molecules with which fibronectin interacts.

INTERACTIONS OF FIBRONECTIN

Plasma fibronectin is known to interact with fibrin and can even be cross-linked to it by factor XIII transglutaminase [27]. Numerous studies have shown that fibronectins interact with collagen, especially when it is denatured to gelatin. In fact, affinity chromatography on gelatin-Sepharose is now the major step in purification of fibronectin [86]. Codistribution of fibronectin and collagen at the cell surface has been reported [87]. Fibronectin can be cross-linked by chemical cross-linked by chemical cross-linkers to sulfated proteoglycans [77], which suggests that it is also in close proximity with them at the cell surface. Fragments of fibronectin with specific affinities for gelatin and glycosaminoglycans have been isolated [50–53]. It therefore seems clear from a variety of lines of evidence that fibronectin can interact through specific binding sites with extracellular macromolecules (collagen, proteoglycans, fibrin). It is also known that fibronectin at the cell surface forms high-molecular-weight aggregates that dissociate on reduction of disulfide bonds [43, 44]. Disulfide bond formation either with itself or with other cell surface molecules is apparently essential for fibronectin to bind to or be retained at the surface [42, 88].

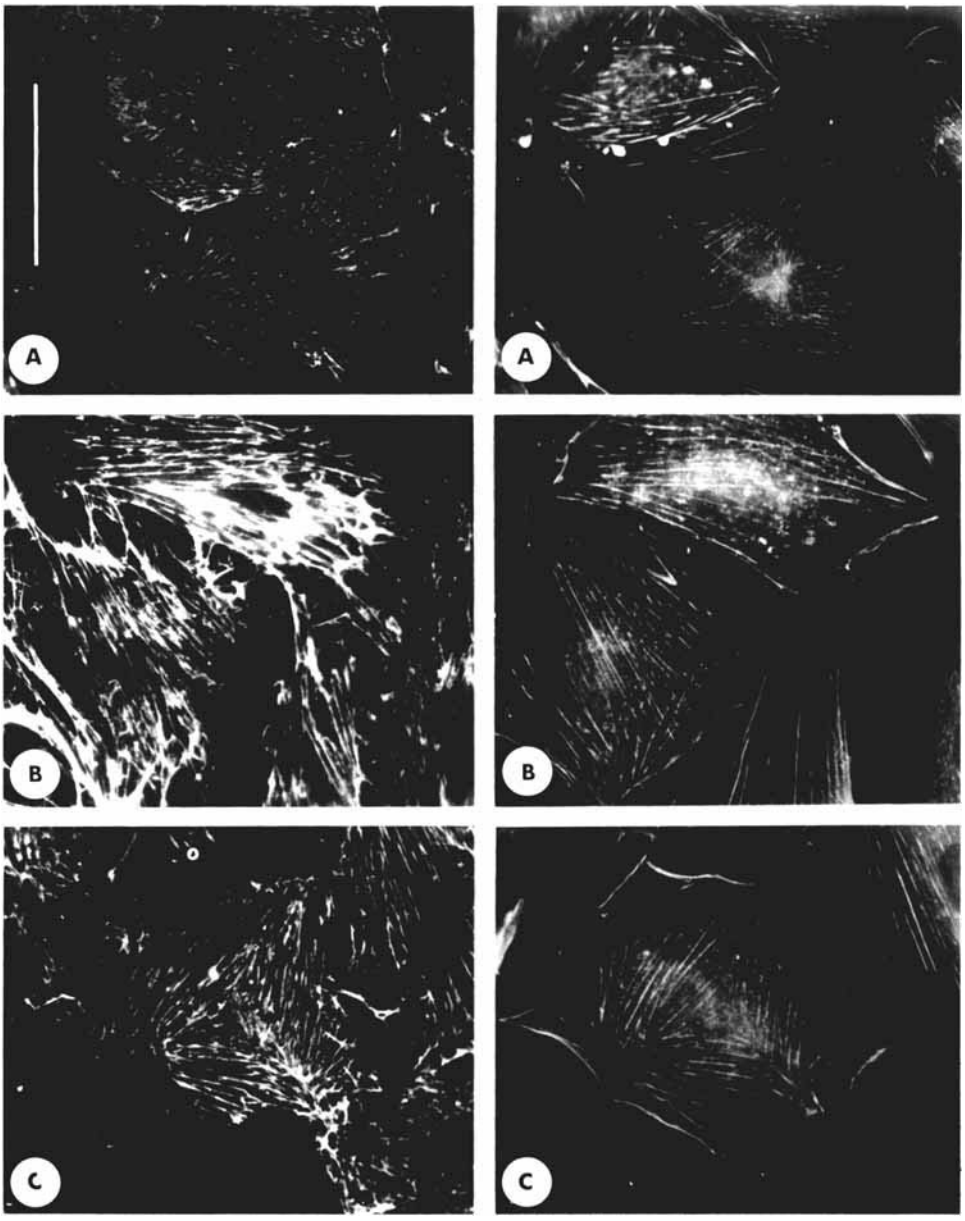

Fig. 3. Double-label immunofluorescence of actin (right) and fibronectin (left). NIL.8 cells were growth-arrested by culture in 0.3% serum, fixed, permeabilized with acetone, and double-stained. Note the correspondences between arrays of actin inside cells and arrays of fibronectin between cells and substratum. Lack of complete identity shows that the antisera do not cross-react. Bar represents 50 μ.

Knowledge of these interactions does not yet provide any insight into the means by which fibronectin might interact with the cytoskeleton, since the latter interaction presumably involves integral membrane proteins. The recent observations that fibronectin may interact with certain gangliosides [89] may be the first indication of interactions with the plasma membrane. It is clear that much research remains to be done in this area, since discovery of the means by which fibronectin binds to the cell surface may lead to an understanding of a) its transmembrane effects, b) the reasons for reduced binding and retention of fibronectin by transformed cells and, therefore, the reasons behind the loss of fibronectin that is associated with transformation and that leads to pleiotropic alterations in cellular phenotype.

CONCLUSIONS

It is now clear that loss of cell surface fibronectin is a frequent correlate of oncogenic transformation. Studies on the relevance of this loss for the behavior of cells in vitro suggest that fibronectin is involved in cell-substratum adhesion and thus has effects on various aspects of morphology and motility that are related to adhesion. The relevance to in vivo parameters is less clear, although many results suggest a correlation with tumorigenicity and most recently with metastasis. The in vitro data that suggest a role for fibronectin in adhesion would be consistent with a role in invasion and metastasis, both of which probably involve alterations in adhesion. One could make plausible arguments extrapolating the in vitro results to the in vivo situation. However, at this point it remains uncertain exactly what role loss of fibronectin plays in vivo, and this will no doubt be a major area of future research.

The many binding affinities shown by fibronectin present an interesting problem in protein chemistry. How are all these binding sites arranged within the large glycoprotein? Their functional relevance has also to be analyzed. One of the more interesting interactions of fibronectin is with microfilaments. The molecular basis of this transmembrane interaction is completely unknown and offers an attractive, if difficult, problem for investigation.

The reasons for loss of fibronectin on transformation also need further analysis. Insights may well arise from analyses of the interactions of fibronectin. There is also the question of regulation of rates of biosynthesis both on transformation and in normal cells that can modulate their rates of synthesis over large ranges.

Fibronectins have provided a fertile area for research over the past five or six years and seem likely to do so for a few years more.

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