REVIEW ARTICLE

Fibronectin: Review of its Structure and Possible Functions

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Soluble fibronectin is a large glycoprotein which is found in blood and other body fluids. Insoluble fibronectin is found in connective tissues and associated with basement membranes. Fibronectin has been known by many other names, including cold-insoluble globulin, α_2-surface binding opsonic protein, antigelatin factor, large external transformation-sensitive (LETS) protein, and cell surface protein. In cell culture, fibronectin is secreted into the media of substrate-attached cells and deposited in the extracellular connective tissue matrix. Collagen, a second component of the matrix, binds to fibronectin. Sulfated proteoglycans, heparin, hyaluronic acid, fibrin, gangliosides, and components of eukaryotic cell surfaces and bacterial cell walls also interact with fibronectin. Fibronectin has been detected in very early embryos of species as distant as the chick, the mouse, and the sea urchin. Thus, fibronectin may have an organizing role in the formation of the extracellular matrix, may act as an adhesive protein for the orderly growth and positioning of cells, and may be an opsonic protein for tissue debris, soluble fibrin, and gram-positive bacteria. In the present review, we attempt to summarize the rapidly expanding literature on fibronectin, particularly in relation to wound healing and tissue repair. A number of reviews have appeared recently which contain more complete references [1–5].

PROPERTIES OF FIBRONECTIN

Some properties of human plasma fibronectin are given in the Table. It is a fast β-globulin with a sedimentation coefficient ($S^0_{20,w}$) of about 13 and a molecular mass, based on sedimentation equilibrium, of 440 kilodaltons (kd). Its frictional ratio is about 1.7. The properties of cell culture fibronectin are similar except that, as discussed below, cell culture fibronectin is 100-fold less soluble than plasma fibronectin in physiological saline. Spectroscopic and hydrodynamic studies in various solvents suggest that both plasma and cell culture fibronectin have globular and flexible regions inasmuch as the sedimentation coefficient can change markedly in the absence of changes in spectroscopic properties.

Soluble fibronectin is a disulfide-bonded dimer of 200 to 250 kd 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. Some laboratories have found that the apparent subunit size (in sodium dodecyl sulfate-polyacrylamide gels) of fibronectin secreted by cells in culture is slightly larger than plasma fibro-

nectin. Fibronectin in amniotic fluid also appears to have a larger subunit than fibronectin in plasma.

Insoluble fibronectin extracted from the cell layer of cultured cells is present as both disulfide-bonded dimers and multimers. Pulse labeling 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. Further studies are needed to determine whether fibronectin in tissue stroma is also composed of disulfide-bonded multimers.

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 nontransformed 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.

MODEL OF FIBRONECTIN BASED UPON PROTEOLYTIC CLEAVAGES

Cleavage of the large polyfunctional fibronectin subunit with a variety of proteases results in fragments which retain one or more properties of the intact molecule (Fig 1). Three regions have been identified. The 27 kd tryptic fragment from the NH_2-terminus is basic, contains F. $XIII_a$ (plasma transglutaminase) reactive glutaminyl residues, binds to S. aureus and to fibrin, and mediates F. $XIII_a$-catalyzed cross-linking to collagen. Strong noncovalent binding to collagen is mediated by the adjacent 30-60 kd region. The COOH-terminal region is responsible for binding the heparin and for cell adhesive activity. The 2 free cysteines per subunit are in the COOH-terminal one-third of the subunit. Dimerization of the subunit is mediated by interchain disulfide(s) at the extreme COOH-terminus.

INTERACTION OF FIBRONECTIN WITH FIBRINOGEN AND FIBRIN

The concentration of fibronectin in serum is 20–50% less than the concentration in plasma; this difference is greater if clotting is carried out at 0–4°C. Loss of fibronectin into the clot at 22–37°C is due to F. $XIII_a$-catalyzed covalent cross-linking (by ϵ-(γ-glutamyl) lysine linkages) between fibronectin and the α chain of fibrin. Loss of fibronectin into the clot at lower tem-

TABLE 1. *Properties of human plasma fibronectin*

Fast β-globulin
pI: 5.5–6.2
$S_{20,w}^{0}$: 12–14 S
Size: 440 kd
Composed of 200 to 220 kd subunits
Approximately 1.6 free cysteine per 200 kd subunit
Carbohydrate content: 4 to 5%
Concentration in normal adult plasma:
    male, 180–720 μg/ml; female, 150–540 μg/ml
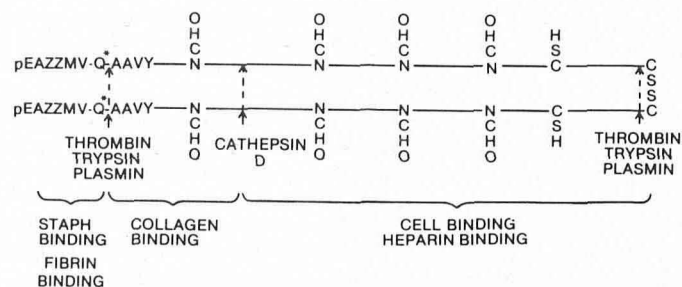Concentration in normal serum: 20–50% less than in plasma

FIG 1. Model of the covalent structure of fibronectin based upon studies of proteolytic cleavage products. Abbreviations: *pE*, pyroglutamic acid; *A*, alanine; *M*, methionine; *V*, valine; **Q*, F. XIII$_a$-reactive glutamine; *Y*, tyrosine; *N*, asparagine; *CHO*, complex oligosaccharide; *CSH*, cysteine; and *CSSC*, cystine; *Z*, glutamic acid or glutamine.

peratures is due to both noncovalent binding and covalent cross-linking. The only other plasma protein known to be incorporated into the clot in a F. XIII$_a$-dependent manner is α$_2$-plasmin inhibitor. Assuming that the concentration of fibrinogen in plasma is 2,400 μg/ml, of which 100% is incorporated into the clot; that the concentration of fibronectin in plasma is 320 μg/ml, of which 35% is incorporated into the clot; and that the concentration of α$_2$-plasmin inhibitor in plasma is 69 μg/ml, of which 24% is incorporated into the clot; the mass of the clot would be 94.9% fibrin, 4.4% fibronectin, and 0.7% α$_2$-plasmin inhibitor.

Fibronectin is necessary for cryoprecipitation of fibrinogen-fibrin complexes, even when the complexes are saturated with fibrin. Fibronectin probably acts as a nucleus, because the ratio of fibronectin:fibrinogen:fibrin in the precipitated complexes is approximately 0.05:0.8:0.2. Such complexes are found in plasma of patients with "cryofibrinogenemia" and chronic disseminated intravascular coagulation. Fibronectin is also necessary for the formation of a precipitate in heparinized plasma at 2°C. Although the heparin-precipitable fraction from normal plasma contains about 65% fibrinogen and 35% fibronectin, the precipitate can be formed from plasma which lacks fibrinogen. In a purified system, the amount of precipitation depends upon fibronectin concentration, heparin concentration, pH, ionic strength, and calcium ion concentration. For a given set of conditions, the amount of precipitation is increased if fibrinogen is also present. Optimal precipitation occurs when fibronectin and heparin are present in a 3:1 (w/w) ratio. The participation of fibrinogen or fibrin in the cryoprecipitation or cold heparin precipitation reactions requires intact α chains; fibrinogen and fibrin molecules which lack the carboxyl terminal region of the α chain are excluded from these precipitates.

Fibronectin which has been cross-linked to fibrin only subtly alters the properties of the clot. Fine clots (i.e., clots consisting of fine fibrils with few branch points, formed at high ionic strength and pH) to which fibronectin is cross-linked at 22°C have half the elastic modulus of cross-linked fine clots which lack fibronectin, whereas coarse clots (i.e., clots consisting of coarse fibrils with many branch points, formed at low pH and ionic strength) to which fibronectin is cross-linked at 22°C have twice the elastic modulus of cross-linked coarse clots which lack

fibronectin. Cross-linking of fibronectin to fibrin, however, profoundly enhances the attachment and spreading of cells on a fibrin-coated substratum. Thus, covalent attachment of fibronectin to fibrin may be important for adhesion and migration of cells into a wound.

INTERACTION OF FIBRONECTIN WITH COLLAGEN AND GLYCOSAMINOGLYCANS

Fibronectin binds and can be cross-linked (by F. XIII$_a$) to several types and forms of collagen. Although there are conflicts in the literature, several generalizations seem true. First, at 4° and 20°C, fibronectin interacts better with denatured collagen and collagen fragments than with native collagen. Second, at 37°C the interaction of fibronectin with native Type I collagen is only at the site of cleavage of collagen by vertebrate collagenase. Because collagenase cleaves the α1(I) chain of Type I collagen in a region which lacks proline and hydroxyproline over a span of 12 residues, there may be local uncoiling of the collagen helix in this region at 37°C. Third, interstitial collagens (Types I, II, and III) interact better with fibronectin than basement membrane collagens (Types IV and V).

There is evidence for interactions of fibronectin with heparin, more heavily sulfated forms of heparan sulfate, hyaluronic acid, and chondroitin sulfate-containing proteoglycan. At 4°C, heparin induces precipitation of plasma fibronectin into filamentous structures. The fraction of heparin which is present in heparin-precipitated fibronectin is not enriched or depleted in anticoagulant activity. Heparin-precipitated fibronectin binds fibrinogen and native collagen. Passage of heparin or heavily sulfated heparan sulfate over a column of gelatin-agarose to which fibronectin has been previously bound strengthens the fibronectin-gelatin interaction. Although hyaluronic acid does not compete for binding of heparin to fibronectin, it is an effective inhibitor of fibronectin-heparin-induced precipitation of native collagen.

The interactions among hyaluronic acid, heparan sulfate, collagen, and fibronectin may be important for cell motility. Adhesive foot*pads* of cultured cells sheared from a substratum are rich in fibronectin and heparan sulfate, whereas hyaluronic acid and chondroitin sulfate are coordinately deposited in foot-*prints* left behind by cells moving over a substratum. These findings indicate that heparan sulfate is involved in adhesion to substratum, perhaps by binding to fibronectin, and that hyaluronate-chondroitin complexes may labilize the footpad adhesions, with subsequent cytoskeletal disorganization and cell movement.

INTERACTION OF FIBRONECTIN WITH CELLS

A variety of cell types adhere to fibronectin which has adsorbed to tissue culture plastic at sites of nonspecific protein adsorption, to fibronectin which has specifically adsorbed to collagen, or to fibronectin which has been cross-linked to fibrin. In each of these systems, soluble fibronectin does not compete with adsorbed fibronectin and does not inhibit cell adhesion and spreading. Thus, suspended cells are unable to "arm" themselves with fibronectin and do not deplete the suspension of soluble fibronectin. The cellular "receptor" for fibronectin may involve a di- or tri-sialoganglioside and a ricin-binding glycoprotein.

The opportunity to adhere to fibronectin seems to be very important for many cell types. For example, being in culture dishes to which fibronectin has been adsorbed allows cytokinesis and growth of rat follicular cells in serum-free medium and migration of transformed hamster fibroblasts. Not all cell types require fibronectin for adhesion, however [6]. Chondrocyte adhesion to type II collagen is stimulated by a protein called chondronectin, which is present in fetal serum and cartilage. PAM 212 epidermal cells attach preferentially to type IV collagen and make an adhesion factor called laminin [7].

INTERACTION OF FIBRONECTIN WITH BACTERIA

Fibronectin binds specifically to *Staphylococcus aureus* but not to *Escherichia coli* or *Mycobacterium butyricum*. Binding of fibronectin to *S. aureus* is only slightly inhibited by denatured collagen and is not inhibited by Protein A, the immunoglobulin binding protein of *S. aureus*. The nature of the bacterial component to which fibronectin binds is not known at present. The interaction of fibronectin with bacteria is of potential importance both for the opsonization of bacteria by soluble fibronectin and the attachment of bacteria to insoluble tissue fibronectin.

INTERACTIONS OF FIBRONECTIN WITH ACTIN AND DNA

Fibronectin binds to coulumns of actin-agarose and DNA-agarose under physiological conditions. Thus, fibronectin is one of the DNA-binding proteins of serum. It is not known whether the cellular compartmentilization of fibronectin, actin, and DNA allows interactions to occur in whole cells. In cultured cells, the distribution of extracellular fibronectin and intracellular actin by immunofluorescence can be remarkably similar. By immunoelectromicroscopy, structures containing the 2 proteins are separated by less than 8–22 nm across the cell membrane. On the basis of these findings, a transmembrane protein has been postulated to link together fibronectin fibrils on the outside of the cell with cytoplasmic actin microfilaments on the inside.

SYNTHESIS AND DISTRIBUTION OF FIBRONECTIN IN CELL CULTURE

Synthesis of fibronectin in culture has been demonstrated for a number of cell types, including fibroblasts, vascular endothelial cells, corneal endothelial cells, smooth muscle cells, astroglial cells, Schwann cells, glomerular cells, intestinal epithelial cells, breast epithelial cells, kidney and liver epithelial cells, hepatocytes, chondrocytes, myoblasts, macrophages, and teratocarcinoma cells. Large amounts of fibronectin are synthesized. For instance, cultures of human embryonic fibroblasts produce about 120 μg fibronectin per mg cell protein per 24 hr. A large percentage (60–95%) of the fibronectin is rapidly secreted into the medium; a smaller percentage remains as trypsin-sensitive extracellular protein in the cell layer. Extracellular fibronectin accumulates in the cell layer of cultured cells in patterns which vary from cell type to cell type. In fibroblast cultures, the earliest fibronectin detectable by immunofluorescence is between the cells and the culture dish and co-distributes with cytoplasmic actin microfilaments. As cells grow to confluence, fibronectin, along with procollagen, accumulates at sites of cell-to-cell contact (Fig 2). Confluent fibroblast cultures have an extracellular fibrillar matrix which reacts with antibodies to fibronectin and types I and III procollagen and collagen (Fig 2) and stains with ruthenium red, a dye which is known to bind to proteoglycans. When human fibroblasts are left in culture for several weeks or are treated with ascorbate, the fibrils become thicker (40–50 nm diameter rather than 10–20 nm) and exhibit 67 nm periodicity when stained by an immunoperoxidase technique for fibronectin or type I procollagen and examined by electron microscopy (Fig 3). Fibronectin is present within the matrix in disulfide-bonded multimers as well as dimers and is susceptible to cross-linking by F. XIII$_a$.

Cultured fibroblasts passing through mitosis lose surface-associated fibronectin and then regain it as they flatten in telophase. Other circumstances which cause rounding of cells, such as transformation or treatment with cytochalsin B, also cause loss of cell surface-associated fibronectin. Loss of fibronectin is presumably due to changes in intracellular actin microfilaments.

Association of cells with a fibronectin matrix has dramatic effects which may be of great pathophysiologic importance. Cultured transformed cells acquire a more normal appearance (but not normal growth control) when a matrix is reconstituted with material extracted from normal cultures. Chondrocytes and myoblasts have fibronectin matrices in their undifferentiated state. These matrices are lost when chondrocytes synthesize type II collagen or myoblasts fuse and form myotubes. Differentiation, however, is blocked when fibronectin matrices are reconstituted with matrix material from fibroblast cultures. The labile state of the chondrocyte phenotype may be of crucial importance in the replacement of cartilage by fibrous tissue in rheumatoid arthritis and osteoarthritis. Confluent vascular and corneal endothelial cells bind but do not take up low density lipoprotein. Failure to take up low density lipoprotein by endocytosis has been correlated with acquisition of a fibronectin matrix between the endothelial cells and substratum and may be a mechanism that prevents fatty degeneration of blood vessels.

DISTRIBUTION OF FIBRONECTIN IN TISSUES

Fibronectin can be visualized by immunofluorescence in the very early embryo, and its pattern changes throughout development. It is present in areas of cell migration, is present (along with types I and III collagen) in differentiating mesenchyme, and is associated with limiting membranes of fully formed organs. It is also present in loose connective tissue. The distribution of fibronectin *in vivo* is compatible with the distribution of fibronectin in cell culture and with fibronectin's putative functions in cell adhesion, cell migration, cell differentiation, and tissue stromal organization.

Within rat and human skin [8–10], fibronectin is absent from stable, differentiated parts of the tissue, such as sebaceous glands or the matrix, medulla, cortex, and cuticles of the hair and the inner and outer root sheaths or the epidermis. Fibronectin is found at sites at which cell division is occurring in contact with an extracellular scaffolding, as in the glassy membrane and connective tissue sheath associated with follicular epithelium, the basement membrane underlying vascular endothelial cells, and the connective tissues surrounding and investing nerve and muscle fibre bundles. At the basement membrane of the dermal/epidermal junction, fibronectin occurs at the plasma membrane of the basal cells and in the lamina lucida. Fibronectin is associated with collagen fibers in dermal connective tissues and is present within the endoplasmic reticulum of dermal fibroblasts.

During experimental wound healing [11] and granuloma formation [12], fibronectin is present in large amounts in fibrin clots and in the regenerating tissue matrix. A marked increase in fibronectin is found in the deep dermis of involved scleroderma skin in parallel with the increase in collagen [13,14]. In affected skin in systemic and systemic lupus erythematosus, there are changes in the distribution of fibronectin in the dermal/epidermal junction and in the papillary dermis [15]. There are fibronectin-negative gaps and slit formation in the dermal/epidermal region, together with fibronectin-positive globular bodies and transport of fibronectin into the epidermis.

FIBRONECTIN AS AN OPSONIN

Following injection of phagocytic material, the phagocytic system is refractory for several hours to challenge by a second phagocytic stimulus. The depression in phagocytic activity is due, at least in part, to depletion of fibronectin. Animals with low fibronectin concentrations do not clear gelatin-coated particles as quickly as animals with normal fibronectin concentrations, and serum with low fibronectin concentration does not support the heparin-dependent binding of gelatin-coated particles to liver slices. Plasma fibronectin, whether measured by the liver slice assay or an immunologic assay, is decreased in patients following major surgery or major trauma and in severely ill patients with evidence of disseminated intravascular coagulation. Depression of fibronectin occurs in Rhesus monkeys with Rocky Mountain spotted fever and in a number of
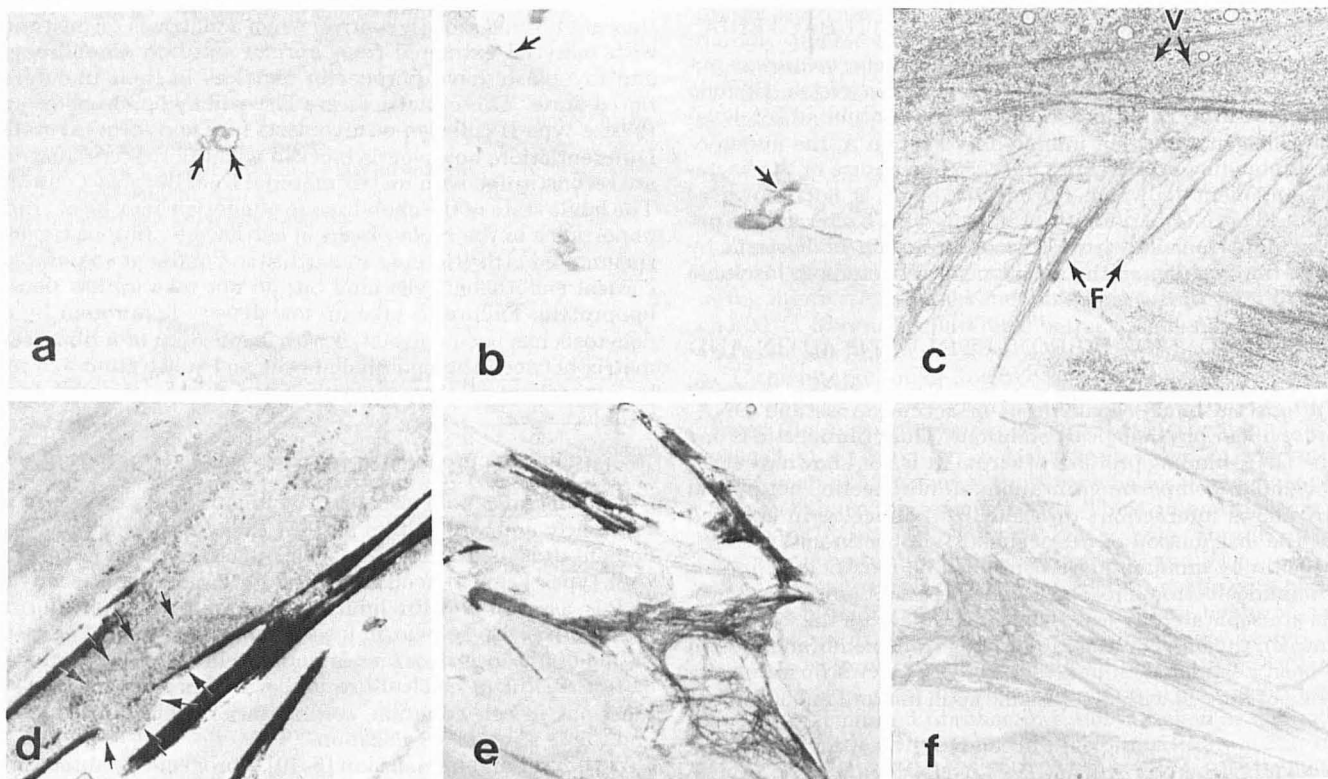
Fig 2. Localization of type I procollagen and fibronectin on young cultured human skin fibroblasts. *a*, Electron micrograph of type I procollagen localization on very low density human fibroblasts. Very small amounts of procollagen type I localization product are present on the surfaces of noncontacting cells. Occasionally small discrete patches of procollagen are seen (*arrows*); however, most membrane surfaces are free of staining (× 3,800). *b*, Electron micrograph of fibronectin localization on very low density human fibroblasts. Patches of nonfibrillar fibronectin are present on the plasmalemma of most cells (*arrows*). The extensive vesicles seen in high density cultures are not present (× 5,500). *c*, Electron micrograph of heavy metal counterstained thin section of young confluent human fibroblasts. The extracellular fibrillar matrix (*F*) has developed. The fibrils are 15–25 nm in diameter and lack periodicity. Many vesicles (*V*) are present near the plasma membrane which is difficult to discern because it is sectioned tangentially parallel to the monolayer (× 6,800). *d*, Ultrastructural localization of procollagen type I on young confluent human fibroblasts. Type I procollagen is present on bundles of extracellular fibrils as well as in a diffuse form on the plasma membrane and in membrane-associated vesicles. The tangentially sectioned membrane is more easily discerned in this micrograph, since it is coated with the diffuse form of localization product (*between facing arrows*) (× 6,700). *e*, Ultrastructural localization of fibronectin on the surface of young confluent human fibroblasts. Fibronectin is present on the extracellular fibrillar matrix, in a diffuse form on the plasma membrane and also in membrane-associated vesicles (seen best in Fig 3*e* and other sections grazing the membrane) (× 5,500). *f*, Electron micrograph of adsorption control for fibronectin localization. No staining is present when antifibronectin is preadsorbed with purified fibronectin (× 3,800).

other experimental models. However, depression of reticulo-endothelial system phagocytic activity may be seen with normal circulating fibronectin concentration, as after endotoxin injections in rats.

Changes in plasma fibronectin concentration are not commonly associated with severe diseases. Fibronectin is not an active phase reactant following myocardial infarction. Fibronectin concentration varies among individuals, and females tend to have lower concentrations than males. Fibronectin concentration is normal in pregnant women, but the concentration can increase several-fold in recurrent cholestasis of pregnancy. Newborns have 35% of the normal adult plasma concentration of fibronectin. Fibronectin is also present in amniotic fluid and cerebrospinal fluid.

The plasma concentration of fibronectin is probably decreased in severely ill patients with disseminated intravascular coagulation because of increased utilization rather than decreased synthesis. Experimental disseminated intravascular coagulation in rabbits causes decreases of both ^{125}I-fibronectin and ^{131}I-fibrinogen; decreases in ^{125}I-fibronectin are not found in animals initially defibrinated with pit viper venom. These findings indicate that fibronectin complexes with fibrin formed by thrombin, but not by pit viper venom, and that the complexes are rapidly cleared from the blood. Fibronectin may mediate the clearance of soluble fibrin by macrophages.

The concentration of plasma fibronectin that is required for normal function is not known. Patients with less than 50% of the normal concentration (150 µg/ml or less) have a higher mortality than patients with normal concentrations. Decreases in fibronectin concentration are strongly associated with decreases in the concentrations of plasminogen and α_1-antithrombin, and it may be premature to attribute mortality in a deficiency of fibronectin. Restoration of fibronectin concentration by giving cryoprecipitate, however, has had sometimes dramatic effects on pulmonary function, limb blood flow, and overall clinical well-being in an ongoing trial.

FIBRONECTIN, PLATELETS, AND ENDOTHELIAL CELLS

Platelets contain 2–4 µg of fibronectin per 10^9 platelets or about 0.5% of the blood's content of fibronectin. Platelet fibronectin is associated with α granules and is released when platelets are stimulated with thrombin or collagen. Upon stimulation of washed platelets, fibronectin can be demonstrated by immunofluorescence on the platelet surface. When washed platelets are allowed to adhere to collagen and then sonicated, platelet proteins remaining attached to collagen after sonication are enriched in fibronectin and cytoskeletal proteins. Preincubation of collagen with plasma fibronectin at 22°C blocks the
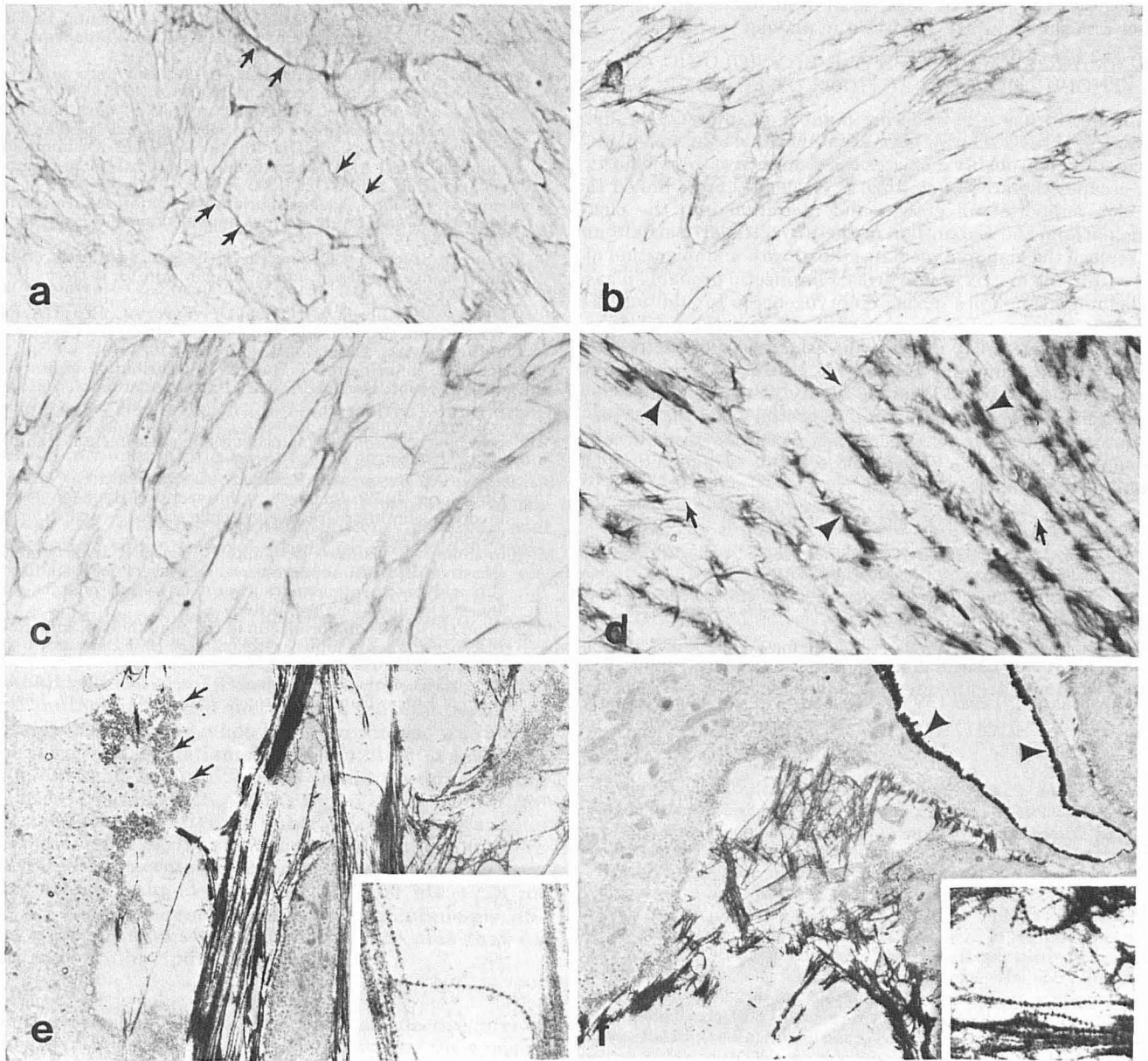
FIG 3. Effect of extended time in culture on type I procollagen and fibronectin distribution in cultures of human skin fibroblasts as visualized by light and electron microscopy. *a*, Young confluent cultures of human fibroblasts (one week old) have a fibrillar distribution of type I procollagen which surrounds fibroblasts. *Arrows* indicate 3 examples of fibrillar staining (× 200). *b*, Young confluent cultures of human fibroblasts have a fibronectin distribution which closely resembles that seen for type I procollagen (× 200). *c*, Old cultures of human fibroblasts (1 mo old) have long lacy arrays of fibrils which stain for procollagen type I (× 200). *d*, Old cultures of human fibroblasts (1 mo old) develop a dense matrix of fibronectin which appears to span between cells (*arrowhead*). A faint staining of the lacy fibrils (as seen in 3c) is also present (*small arrows*) (× 200). *e*, By electron microscopy, type I procollagen in 1 mo old culture is present in fibrils which have the characteristic morphology of mature collagen fibrils (see *insert*). The fibrils have a 67 nm axial periodicity and are quite long, coursing in a fashion parallel to the fibroblasts. Staining for type I procollagen is also present in a diffuse manner on the plasmalemma (*arrows*) and in membrane-associated vesicles (× 5,000, *insert* × 15,000). *f*, By electron microscopy, fibronectin in 1 mo old cultures coats membrane surfaces as short fibrils which extend perpendicularly from the surface (*arrowheads*). Other membrane surfaces have the diffuse staining characteristic of confluent cultures. Vesicular staining is present. Longer fibrils are stained, some of which have 67 nm axial periodicity (*insert*). In other micrographs, the longer, periodic fibrils are more prevalent (× 5,000, *insert* ×·15,000).

ability of the collagen to induce release of serotonin from washed platelets. These findings suggest a pathway in which fibronectin is secreted from platelets, binds to the platelet surface, and mediates collagen-platelet adhesion and further stimulation of platelets by collagen. However, preincubation of washed platelets with gelatin only slightly reduces the binding of platelets to collagen in a quantitative adhesion assay, and the sequence of the region of the α1(III) chain of type III collagen which is most active in platelet adhesion does not resemble the sequence about the collagenase cleavage site of type I collagen which is recognized by plasma fibronectin. Further, plasma fibronectin enhances rather than inhibits spreading of platelets on collagen-coated surfaces. Finally, a family with Ehlers-Danlos syndrome has been described in which platelet aggregation by collagen is enhanced when purified plasma fibronectin is added to the patient's platelet-rich plasma [16]. These findings seem to rule out any simple model in which cell surface fibronectin is a "receptor" for collagen but

suggest that the pools of fibronectin in platelets, plasma, and vessel wall somehow are important in platelet reactions.

SUMMARY OF THE POSSIBLE PHYSIOLOGIC AND PATHOPHYSIOLOGIC ACTIONS OF FIBRONECTIN

Fibronectin has a bewildering number of interactions and possible functions. During and after the final stage of blood coagulation, it probably mediates the clearance of soluble fibrin that escapes the area of clotting, is covalently cross-linked to the clot, supports cell growth and migration into the clot, participates in the elaboration of the extracellular matrix that will replace the clot, and mediates the growth and migration of cells within the matrix as it evolves. Fibronectin probably plays similar important roles during embryogenesis. In addition, fibronectin may opsonize gram positive bacteria and debris in devitalized tissues, may mediate the attachment of bacteria to damaged tissues, and may help mediate the activation of platelets by damaged tissues. Some severely ill patients have decreased plasma concentrations of fibronectin. Thus, the increasing information about fibronectin has given new insights into the adhesive properties of cells and a better understanding of wound healing and tissue repair.

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