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STUDIES ON FIBRONECTIN IN THE SKIN: VI. INTRA-EPIDERMAL DEPOSITIONS IN VULGAR PSORIASIS, LUPUS ERYTHEMATOSUS, BULLOUS PEMPHIGOID AND DERMATITIS HERPETIFORMIS

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Abstract. The fibronectins are a group of glycoproteins present in plasma and cellular tissues. They are produced by fibroblasts and endothelial cells, and are of importance in cellular adhesion and spreading. Fibronectin has a special affinity to fibrous proteins such as collagen and elastin, and is abundantly present in normal skin in the dermo-epidermal junction area, dermis, and subcutis. Fibronectin is not found in the epidermis. In a number of diseases fibronectin can be demonstrated in the epidermis of lesional skin, with or without affection of the dermo-epidermal junction area. Such changes are found in psoriasis vulgaris, lupus erythematosus, bullous pemphigoid and dermatitis herpetiformis, and represent the exoscrosis of plasma and/or transepidermal elimination of degenerated tissue structure with fibronectin from the dermo-epidermal junction and the papillary dermis.

Key words: Fibronectin; Skin; Psoriasis vulgaris; Lupus erythematosus; Bullous pemphigoid; Dermatitis herpetiformis

Fibronectin represents related, possibly identical, glycoproteins of human plasma and cellular tissues. Plasma fibronectin, also called cold-insoluble globulin, is active in hemostasis (16), in host defence (4), and in the formation of the "heparin precipitable fraction" (12). Cell surface fibronectin is important in the adhesion and spreading of cells (19) and in its affinity to fibrous proteins such as collagen (5).

Cellular fibronectin is produced mainly by fibroblasts, astroglial and endothelial cells (3). In immunofluorescence studies, fibronectin is found in embryonic and adult tissue. It is located as extracellular fibrils in the connective tissue, in primitive mesenchyme and in basement membranes (14).

In normal human skin, fibronectin is present in the dermo-epidermal junction (DEJ) area, in the dermis and subcutis (7). A variation of the normal skin pattern has been described in various skin diseases (8, 9, 10, 11).

Fibronectin has not been found in the epidermis of normal and non-lesional skin, in contrast to lesional skin in psoriasis, lupus erythematosus, bullous pemphigoid and dermatitis herpetiformis. In these diseases, intra-epidermal depositions of fibronectin have been demonstrated, and a closer presentation of these findings is reported in the present study.

MATERIALS

Biopsies were taken from lesional and non-lesional skin from all patients. The following groups were investigated: 10 patients (5 women, 5 men) with psoriasis vulgaris, 12 patients (5 women, 7 men) with lupus erythematosus (LE), 5 male patients with dermatitis herpetiformis (DH), 8 patients (3 women, 5 men) with bullous pemphigoid (BP), and a control group of 10 non-dermatological patients (6 women, 4 men).

In the LE group, 2 patients demonstrated systemic LE, and 10 patients had the chronic discoid type.

METHODS

Cryostat-cut skin sections were investigated with an indirect immunofluorescence (IF) technique using a specific antiserum against plasma fibronectin (cold-insoluble globulin), as previously described (7). Serial sectioning of the samples was performed to exclude the possibility of dermal papillary structures in the epidermal area.

RESULTS

Normal and non-lesional skin

All groups investigated demonstrated the same IF pattern in normal and in non-lesional skin samples. In the epidermis no specific IF for fibronectin was observed. In the DEJ area, a continuous linear staining was found, together with a reticular stain-

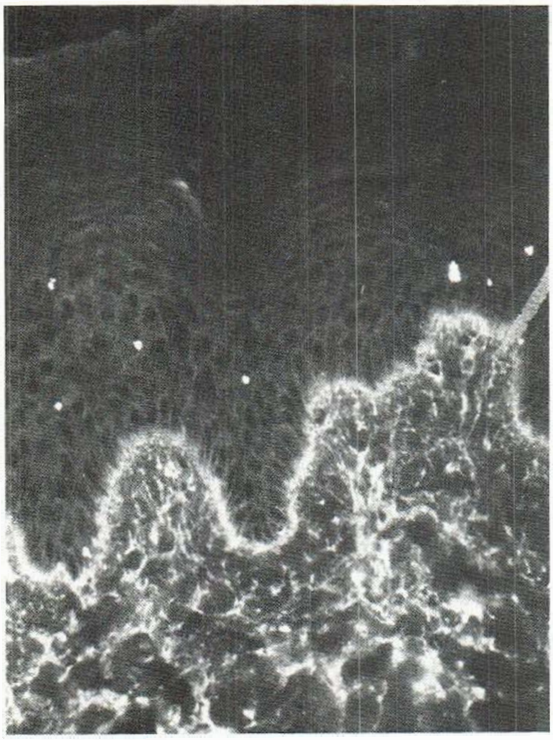

Fig. 1. Immunofluorescence pattern in normal skin.

Fig. 2. Intra-epidermal deposit in psoriasis.

ing in the papillary dermis and a fibrillar staining in the reticular dermis (Fig. 1).

Lesional skin

Psoriasis vulgaris. Epidermal staining for fibronectin was demonstrated in circumscribed areas of the sections, mostly located above dermal papillas protruding up to the cronified layers (Fig. 2). The IF pattern was consistent with an intercellular deposition, showing punctated linear structures, together with more dense depositions probably located in the cytoplasma of keratinocytes. In some papillas, a diffuse IF was seen from the papillary tips into the epidermis, being concentrated in the cornified layers.

In the DEJ and dermis, no apparant changes in IF pattern differing from that of unaffected skin could be observed.

Lupus erythematosus. In areas of affected skin demonstrating changes of the normal fibronectin structure, intra-epidermal deposition of fibronectin was found (Fig. 3). This was first observed above tips of dermal papillas, showing a pronounced IF pattern with loss of the reticular structure of the papillary dermis. In areas of more pronounced disintegration of fibronectin, formation of IF-positive, bud-like extensions and globular droplets into epidermis was found (Fig. 4). Intra-epidermal deposits of fibronectin were located inter- and intracellularly, showing a low concentration in lower layers but increased higher up in the epidermis. Apart from a dust-like IF pattern in the lower epidermal areas (Fig. 3), a diffuse and homogeneous IF pattern could be observed. Intracellular deposition of fibronectin was a prominent feature, showing a cytoplasmatic staining and leaving a round central nucleus-like structure free (Fig. 5). Often dominant in the histological sections, the cellular structures of such areas may get lost, resulting in diffuse and homogeneous IF material.

Bullous pemphigoid. Intra-epidermal deposits of fibronectin were located in areas with blister reactions where changes in the fibronectin pattern of the DEJ and the papillarly dermis was observed with hazy and distintegrated structures and a condensed IF in the papillary dermis. In these areas, fibronectin was diffusing from the papillary tips up to the blister cavity. Here, stained cellular structures were

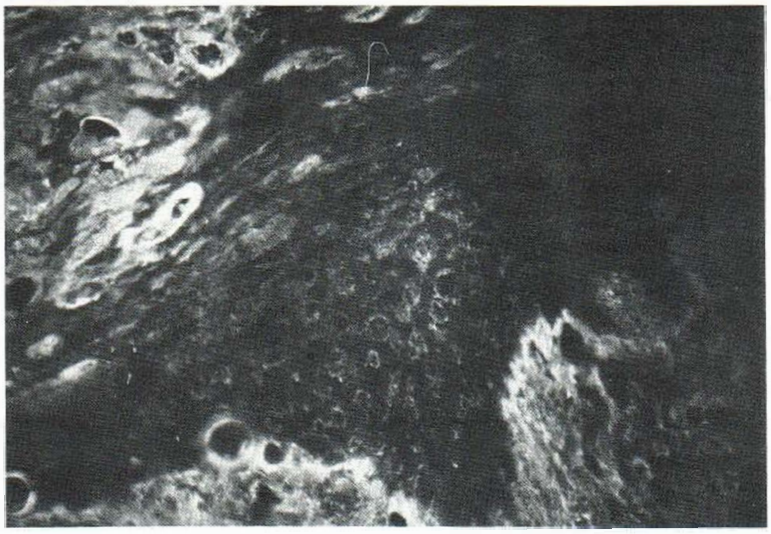

Fig. 3. Intra-epidermal transport from dermis into epidermis in LE.

observed, probably representing acantholytic cells, together with fibrous elements also showing diffuse IF staining.

Dermatitis herpetiformis. In affected skin, intra-epidermal deposition of fibronectin was regularly found (Figs. 6, 7). In areas with only minor changes in the distribution of fibronectin, diffusion of fibronectin in the form of intercellular streaks or diffuse cloudy structures in the lower parts of the epidermis was found above tips of dermal papillas. IF-positive globular droplets rose from disintegrated fibronectin structures in the DEJ area into the stratum corneum area (Fig. 6), in either a diffuse or a globular pattern, with an inter- and intracellular distribution.

In slit- and blister formations, rising mainly from the tips of affected dermal papillas, IF-positive fibrous elements were demonstrated. In such blister formations, fibronectin from the DEJ and the papillary dermis was found mainly at the bottom of the blister cavity.

DISCUSSION

Intra-epidermal depositions of fibronectin in the present study are probably derived from two different sources: either from *exoserosis of plasma* from the papillary capillaries into the skin, or from *degeneration of fibronectin tissue* in the DEJ and

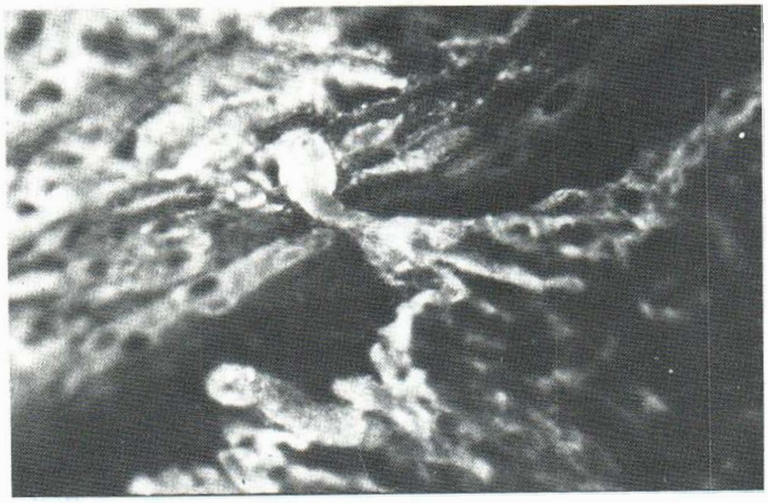

Fig. 4. Epidermal engulfing of bud-like material from dermo-epidermal junction in LE.

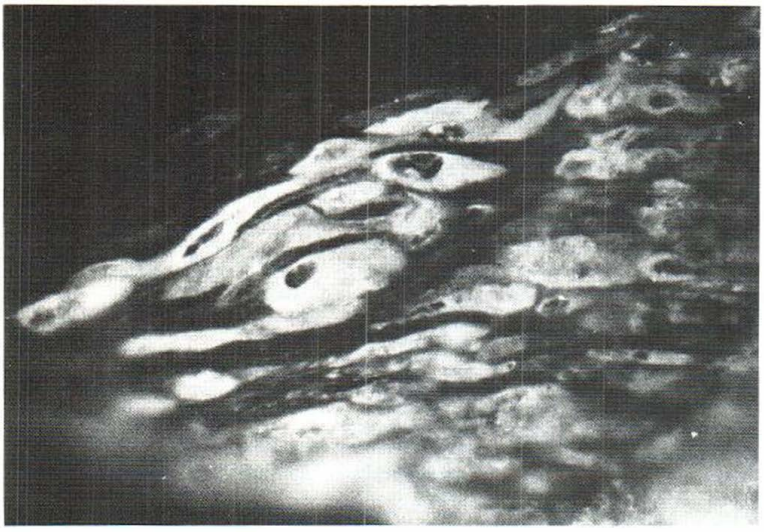

Fig. 5. Intra-epidermal deposition in keratinocytes in LE.

the papillary dermis. Exoserosis of plasma is a pathogenetic feature observed in various skin diseases such as vulgar psoriasis. In this disease, no structural changes of fibronectin in the DEJ area or in the dermis are observed. Consequently, intra-epidermal depositions of fibronectin indicate its origin from plasma.

In DH, the picture is different. One of the first signs of this disease is edema and deposits of fibrin at the papillary tips and deposits of immunoglobulins and complement at the DEJ. In the present study, a change in the morphological structure of tissue fibronectin was demonstrated with the formation of globular bodies containing fibronectin. Diffusion of fibronectin from these structures into the epidermis is observed, probably being derived from plasma as well as from the tissue. In BP, the changes at the DEJ area are comparable to those found in DH. This is also reflected in the present studies for fibronectin. The importance of plasma exoserosis in BP in the deposits of fibronectin in the epidermis is not known. In the formation of blisters, fibrin deposits are abundantly demonstrated in the blister fluid. IF studies also demonstrate fibronectin in these areas, and probably much of the fibrin and the fibronectin material is derived from plasma. In addition, degeneration of tissue fibronectin at the DEJ and the papillary dermis probably accounts for

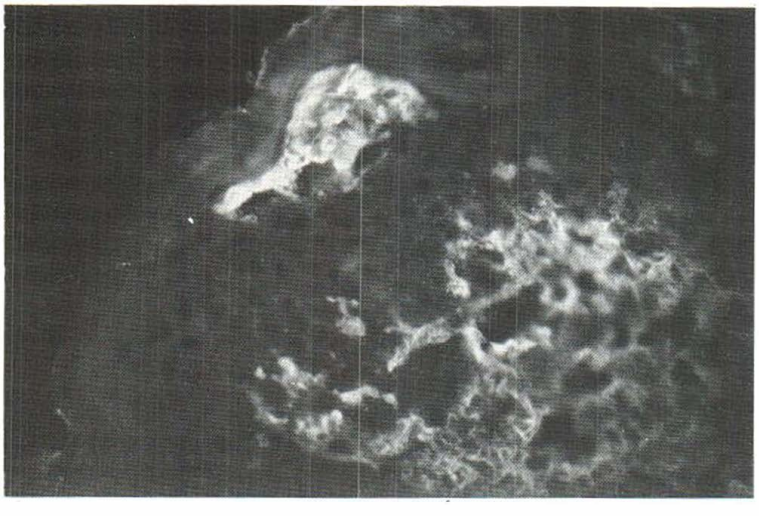

Fig. 6. Intra-epidermal deposition and degenerating structures at the dermo-epidermal junction in DH.

Fig. 7. Intra-epidermal deposition and changes in the dermis in DH.

much of the intra-epidermal deposition of this protein. Compared with DH, the diffusion of fibronectin in BP from the tips of the papillas seems to be oriented mainly into the blister area.

In LE, intra-epidermal deposition of fibronectin is also demonstrated. Fibronectin seems to diffuse or become expellled as droplets from degenerated structures in affected skin at the DEJ and the papillary dermis, being subsequently transported into the epidermis. In DH, BP and LE, a degenerating influence on fibronectin structures is always observed in areas with intra-epidermal deposition of fibronectin. Very similar changes are also observed in lichen planus (9) with the formation of globular droplets containing fibronectin, but without further transport of this portein into the epidermis.

Subsequently, two types of intra-epidermal deposition of fibronectin are possible: (1) In DH, BP and LE, degeneration of tissue elements at the DEJ and in the dermis is observed with consecutive changes in the distribution of tissue fibronectin, and (2) exoserosis of plasma containing plasma fibronectin (cold-insoluble globulin) in diseases such as psoriasis vulgaris, without degenerating changes in the fibronectin tissue structures. In DH, BP and LE, both mechanisms are probably at work.

In normal and unaffected skin, no intra-epidermal deposition of fibronectin is observed. The pathogenetic significance of such deposition is unknown, but possibly represents the expulsion of unwanted material from the skin. A similar mechanism was described by Kyrle (13) as hyperkeratosis follicularis et parafollicularis in cutem penetrans. Freudenthal (6) found that amyloid is expelled through epidermis, and the same process has been observed in various "perforating" diseases such as elastosis perforans serpinginosa, reactive perforating collagenosis and perforating folliculitis (15). In contrast to granulomatous disorders such as granuloma annulare (1, 18) and necrobiosis lipoidica (17), this has not been reported in the diseases investigated in the present study.

Mehregan described in 1970 a phenomenon called transepithelial elimination, meaning transport of foreign material from the connective tissue, often as a result of tissue damage, through the epidermis and out of the organism. Transepidermal elimination of fibronectin in the present investigation is performed by transport of fibronectin by intercellular diffusion and with intracellular phagocytosis by keratinocytes. In a study by Bayoumi, Gaskell & Marks (2), subepidermally deposited charcoal particles in guinea pigs resulted in transepidermal elimination within 4 days. The ability of epidermal cells to phagocytose is reported by Wolf & Konrad (20), and phagocytosis of melanosomes is a wellknown physiological phenomenon of these cells.

Because of disease processes resulting in degeneration of structures containing fibronectin, this material must be removed from the skin. This is accomplished by transepidermal elimination, probably in a number of diseases affecting fibronectin structures in the DEJ and the upper part of the dermis. Whether or not fibronectin also has other biological implications in epidermal cells is at present uncertain. The opsonic qualities of this protein as described by Blumenstock, Weber & Saba in 1977 (4) should be kept in mind.

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