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Detection of Transferrin and C3d Receptors in the Skin of Patients with Various Dermatoses

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The localization of transferrin and C3d receptors in various skin lesions and normal appearing skin have been studied on sections with the PAP technique.The transferrin receptor was recognized in the lower epidermis from psoriatic plaques. Here it was more evident than in other inflammatory or hyperproliferative disorders where it was mainly detected on the basal cells. In healthy skin or lesions of lichen planus, scleroderma and ichthyosis the transferrin receptor was not detected in the epidermis. The C3d receptor was in normal skin found on the basement membrane and on elastic fibres in the papillary dermis. The basement membrane was strongly marked in pemphigoid but was not seen in lichen planus and Ehlers-Danlos syndrome. In patients with urticaria factitia, contact dematitis, psoriasis and Darier's disease the suprabasal cells also expressed C3d whereas in other dermatoses the epidermis was negative. Colloid bodies in lichen planus and GVH reactions expressed both the transferrin receptor and C3d.

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Transferrin receptors have been found in proliferating cells, where they bind transferrin-iron complexes, which are essential for cell growth. In normal human skin the receptors have been detected on the outer root sheaths of the hair and in the eccrine and sebaceous glands. In two studies monoclonal antitransferrin antibodies also labelled the basal cells of normal skin (1, 2), but other authors have reported a very weak or no labelling of the basal cells (3, 4). The presence of transferrin receptors has also been demonstrated in various malignant tumours of the skin (see 2 for references). In psoriatic skin the receptor was recognized in the whole epidermis, although it was more marked in the basal layer (3).

The third component of the complement system has a degradation product C3d (35 kD) which has important immunobiological functions and might also act as a lymphocyte growth factor (5). C3d expresses the binding site for CR2, detected mainly on B lymphocytes (6). The C3d receptor has been recognized on the epidermal basement membrane zone of normal human skin on the base of the lamina densa and in the sublamina densa region (6–8). It was also detected on elastic fibres and blood vessels (6–7). The C3d receptor has been found to be absent in patients with C3d deficiency (8), but otherwise little is known about its distribution in the skin.

To gain better understanding of the role of these two receptors, their presence in lesional skin of patients with various dermatoses has been investigated in the present study with an immunochemical technique.

MATERIAL AND METHODS

Punch biopsy specimens (3 mm) were obtained from five healthy subjects and from lesions of three patients with psoriasis, four with urticaria factitia, four with chronic urticaria and one each with the following disorders: lichen planus, acute contact dermatitis, prurigo nodularis, pityriasis rosea, graft versus host (GVH) reaction, necrobiosis lipoidica, lichen amyloidosus (treated and non-treated area), basaloma, ichthyosis vulgaris, keratosis follicularis (Darier's disease), drug exanthema, scleroderma, solar urticaria, cold urticaria, discoid lupus erythematosus bullous pemphigoid, benign familial chronic pemphigus (Hailey-Hailey disease), and cutis hyperelastica (Ehlers Danlos syndrome type III). None of the patients had been exposed to UV-B irradiation or used any systemic treatment or topical corticosteroids the last 3 weeks.

The biopsies were quick-frozen in isopentane at -70°C and stored at the same temperature until sectioned in a cryostat. Acetone-fixed sections 6 μm thick were investigated for binding of the monoclonal antibodies, antitransferrin receptor (dilution 1/20, Becton Dickinson Corp, Sunnyvale Calif, USA) and anti-C3d receptor (=CD21 dil 1/100 Dakopatts, Glostrup, Denmark), using the peroxidase-antiperoxidase (PAP) technique (9). Monoclonal anti-HLA-DR or anti-Leu 6 antibodies were used as positive controls. Omission of the primary antibodies served as negative controls.

RESULTS

In healthy skin and apparently normal skin from patients with psoriasis and dermographism, the antitransferrin receptor was only expressed on the hair-root sheaths, sebaceous glands and sweat glands. The

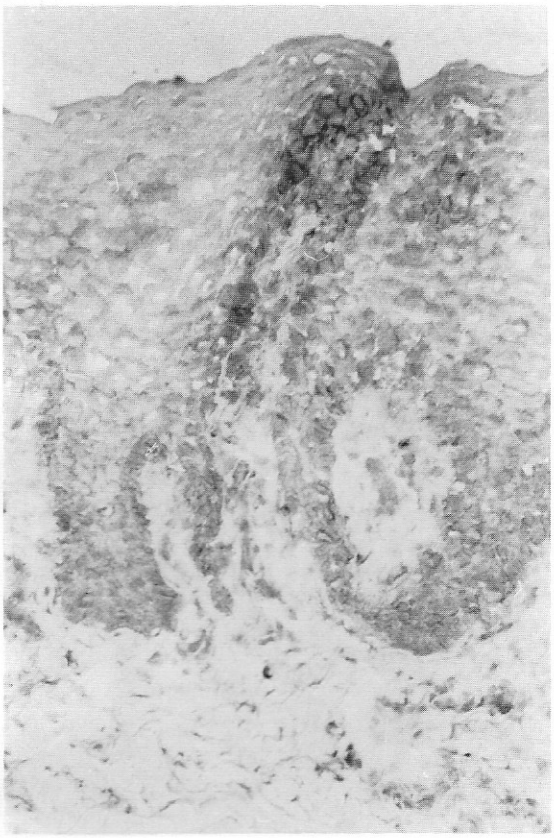

Fig. 1. Transferrin receptors expressed on epidermal cells in a psoriatic plaque ×180.

Fig. 2. Transferrin receptor expressed on dermal cells in necrobiosis lipoidica ×180.

same was found in patients with lichen planus, prurigo nodularis, ichthyosis vulgaris, scleroderma, Ehlers-Danlos syndrome and Hailey-Hailey disease. The antitransferrin receptor was recognized, however, on the lower epidermal cells in lesional skin of patients with psoriasis (Fig. 1). In non-treated lichen amyloidosus, necrobiosis lipoidica, Darier's disease and GVH reaction, it was found mainly on the basal cells. In GVH reaction the colloid body-like structures below the epidermis also expressed the antitransferrin receptor. In necrobiosis lipoidica and pityriasis rosea it was strongly expressed on cells in the dermis (Fig. 2). Weak expression of the transferrin receptor was seen on basal cells in, especially, the upper part of the papilla from lesional skin of patients with acute contact dermatitis, discoid lupus erythematosus and chronic urticaria. In the basaloma only the areas in between the groups of cancer cells reacted.

In healthy subjects the C3d receptor was detected on the basement membrane, on elastic fibres in the papillary dermis and on vascular structures (Fig. 3). The basement membrane showed the most marked expression of C3d in a patient with bullous pemphigoid where it extended in between the basal cells (Fig. 4). Here it was not detected in lesions of patients with lichen planus or Ehlers-Danlos disease. In the papillary layer homogeneous structures resembling the colloid bodies expressed C3d in patients with lichen planus, necrobiosis lipoidica and GVH reaction (Fig. 5). In the epidermis the suprabasal cells expressed the C3d antibody in patients with urticaria factitia, psoriasis, contact dermatitis and Darier's disease (Fig. 6). Weak suprabasal expression of C3d was observed in a patient with GVH reaction. In the lesions of the other disorders investigated the epidermis was always negative.

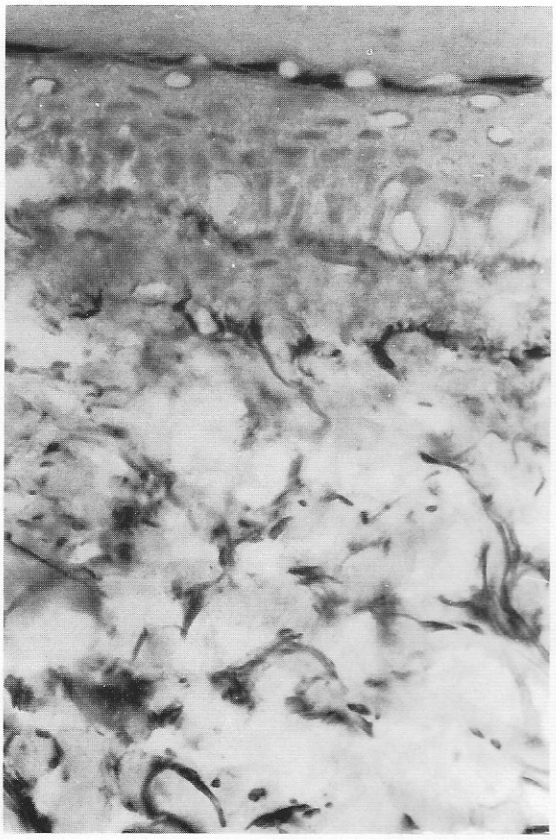

Fig. 3. C3d receptor expression on the basement membrane and elastic fibres in papillary dermis from healthy subjects. ×450.

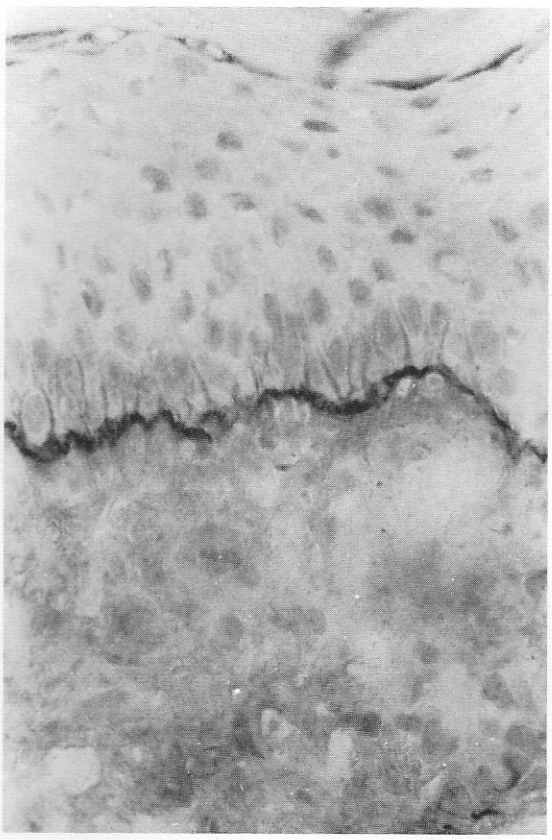

Fig. 4. Marked expression of C3d receptor on the basement membrane and in between basal cells from a patient with bullous pemphigoid. ×450.

DISCUSSION

The expression of the transferrin receptors in the lower epidermis in psoriatic lesions is in accordance with the recent findings of Iwata et al. (3). This expression was more marked than in any of the other disorders investigated, where it was strictly localized to the basal cells and in some lesions, both hyperproliferative and inflammatory, was often weak or totally absent. Only in malignant skin tumours (except basalioma) has such strong expression of transferrin receptor been documented (1–3). A possible reason for the stronger expression of this receptor in psoriasis than in other dermatoses might be that the proliferation is much greater or that we are dealing with a special type of inflammation. Transferrin is known to stimulate the growth of most cultured cells and its uptake is increased in tumours, which could also be of importance in this context (11).

Why some authors have found the transferrin receptor in the basal cells of normal skin is still uncertain (1–2). The discrepancies might reflect the fact that the transferrin receptor consists of a family of molecules that are structurally related but antigenically different (4).

The expression of C3d in the suprabasal cells in lesions of urticaria factitia, contact dermatitis, Darier's disease and GVH reaction, in contrast to its absence in normal skin and several other disorders, merits further investigation. We know that C3 can be produced by the keratinocytes (11) and it is tempting to speculate that some of its cleavage products could be responsible for the positive dermographism. Similar mediators might also explain the expression of C3d in contact dermatitis and Darier's disease. In other disorders such as psoriasis no such expression

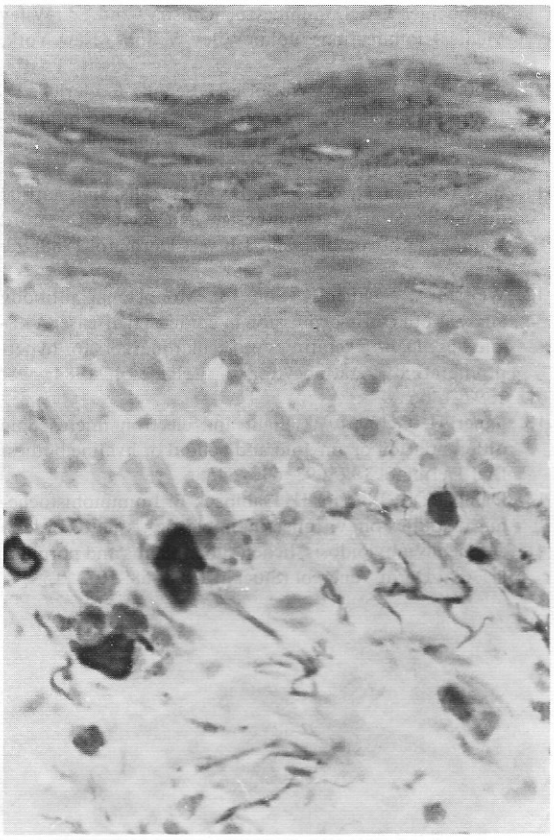

Fig. 5. Colloid bodies and elastic fibres expressing C3d in a patient with GVH reaction. ×450.

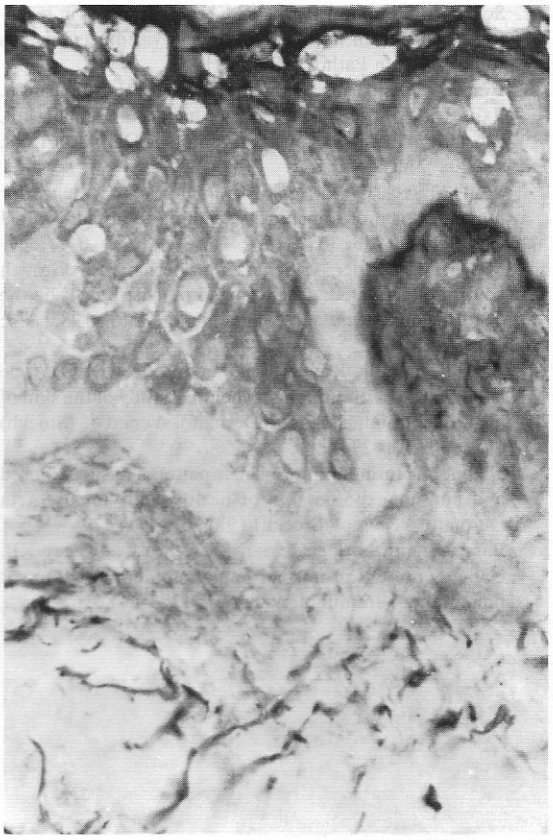

Fig. 6. C3d receptors expressed on the suprabasal cells of the epidermis, basement membrane and elastic fibres from a patient with urticaria factitia. ×450.

was evident. With two different monoclonal antikeratin antibodies, however, suprabasal expression of certain keratins can be seen in hyperproliferative diseases such as psoriasis (12).

The colloid or Civatte bodies are assumed to be formed from degenerating epidermal cells eliminated into the corium (13). They are located in the epidermal-dermal junction and can be detected by antibodies to both vitronectin and serum amyloid P component (14). In both lichen planus and GVH reaction such structures have now been found also to express the transferrin receptor and C3d.

The presence of C3d in the epidermal basement membrane of normal human skin is well established (8). The marked expression in a patient with pemphigoid is consistent with the well known presence of C3d in the basement membrane zone in this disorder. Interestingly, C3d was also found to extend somewhat in between the basal cells. The lack of expression of C3d in lichen planus can be due to the damage of the basal layer. The lack of its expression on the basement membrane in a patient with Ehlers-Danlos syndrome could be part of the quantitative collagen deficiency in this disorder, a possibility which needs to be confirmed in other patients.

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REFERENCES

1. Gatter KC, Brown G, Trowbridge IS, Woolston RE, Mason DY. Transferrin receptors in human tissues, their distribution and possible clinical relevance. J Clin Pathol 1983; 36: 539–545.

2. Soyer H-P, Smolle J, Torne R, Kerl H. Transferrin receptor expression in normal skin and in various cutaneous tumors. Cutan Pathol 1987; 14: 1–5.
3. Iwata M, Otsuka F, Watanabe S, Nogit T, Ishibashi Y. Expression of transferrin receptor in normal human skin, psoriatic skin and various skin tumors. J Dermatol 1988; 15: 208–211.
4. Wells M, Yeh C-I G, Hsi B-L, Faulk WP. Evidence for polymorphism of transferrin receptors in human skin. J Clin Pathol 1986; 36: 1415–1416.
5. Melchers F, Erdei A, Schulz T, Dierich MP. Growth control of activated, synchronized murine B cells by the C3d fragment of human complement. Nature 1985; 317: 264.
6. Baart de la Faille-Kuyper EH, van der Meer JB, Baart de la Faille H. An immunohistochemical study of the skin of healthy individuals. Acta Dermatol Venereol (Stockh) 1974; 54: 271–274.
7. Nieboer C. Immunofluorescence patterns in sun-exposed and not sun-exposed skin of healthy individuals. Acta Dermatol Venereol (Stockh) 1981; 61: 471–479.
8. Basset-Seguin N, Dersookian M, Cehrs K, Yancey KB. C3d,g is present in normal human epidermal basement membrane. J Immunol 1988; 141: 1273–1280.
9. Sternberger LA. Immunocytochemistry, 2nd ed. Wiley Medical Publications, John Wiley & Sons, New York, 1979.
10. Aulbert E, Disselhoff W, Sorje H, Schultz E, Gericke D. Lysosomal accumulation of 67 Ga-Transferrin in malignant tumours in relation to their growth rate. Eur J Cancer 1980; 16: 1217–1232.
11. Basset-Seguin N, Yancey KB. A431 cells and normal human keratinocytes synthesize and secrete the third component of complement. J Invest Dermatol 1988; 90: 546.
12. Weiss RA, Eichner R, Sun TT. Monoclonal antibody analysis of keratin expression in epidermal disease. A 48- and 56-k Dalton keratin as molecular markers for hyperproliferative keratinocytes. J Cell Biol 1984; 98: 1397–1406.
13. Egner H, Gebhart W. Light and electron microscopic differentiation of amyloid and colloid or hyaline bodies. Br J Dermatol 1975; 92: 637–645.
14. Dahlbäck K, Löfberg H, Dahlbäck B. Immunohistochemical studies on vitronectin in elastic tissue disorders, cutaneous amyloidosis, lichen ruber planus and porphyria. Acta Derm Venereol (Stockh) 1988; 68: 107–115.