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Invited Review

Nonerythroid membrane skeletal proteins in normal and diseased human skin

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Summary. A number of reports have described the presence and localization of membrane skeletal proteins in nonerythroid tissues and cultured cells. Interactions of these proteins, which have been extensively characterized in erythrocytes, may be physiologically important in other cell types. This review focuses on recent developments concerning proteins analogous to erythrocyte spectrin, protein 4.1, adducin and ankyrin in epidermal keratinocytes, and discusses their significance from physiological and pathological stand points. Keratinocyte proteins are involved in a wide variety of functions such as the cell-to-cell and cell-to-substratum adhesion, stratification, and maintenance of the cell shape. In epidermal keratinocytes, these nonerythroid membrane skeletal proteins may play a role in maintaining the polarity of membrane proteins by connecting them to the cytoskeleton, regulating cell-cell interdigitations and stabilizing newly synthesized cell membranes before elaboration of cell-cell interdigitations. Furthermore, altered expression and distribution of these proteins may be important in the pathogenesis of skin disease such as psoriasis.

Key words: Membrane skeleton, Erythrocyte, Protein 4.1, Epidermal keratinocytes, Psoriasis

Introduction

Erythrocyte membrane has served as a model system for the investigation of biological membrane structure. As a result of this long-standing interest in the erythrocyte, the membrane-protein interactions at its cytoplasmic surface have been well characterized. This submembranous architecture is referred to as membrane skeleton and is thought to be important in maintaining cell shape and mechanical properties, and in regulating the lateral mobility of transmembrane proteins (Bennet, 1985, 1990). In the erythrocytes, this function is fulfilled by a set of proteins including spectrin, actin, protein 4.1, adducin and a number of other less abundant associated polypeptides which interact with each other and with transmembrane proteins. These proteins create a tridimensional network which stabilizes the overlying plasma membrane (Fig. 1). With the discovery of membrane skeletal protein analogues in keratinocytes and other tissues, the structure of erythrocyte membrane skeleton has gained increased relevance for the study of the molecular organization of the cytoskeletons in more complex cells, and these membrane skeletal proteins are now recognized to play important roles in nonerythroid tissues, including keratinocytes.

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Erythroid and nonerythroid membrane skeletal proteins

The major protein of the erythrocyte skeleton is spectrin, which is a heterodimer composed of a 240 kDa (α) and a 220 kDa (ß) subunit. Two heterodimers linked head to head form a tetramer which is oligomeric form of spectrin in situ. The spectrin fibers are anchored to the membrane through interactions with other cytoskeletal proteins, such as the ankyrin family of proteins and protein 4.1. There is now abundant evidence that spectrin and spectrin-like proteins are not confined solely to the erythrocyte but are widely distributed in different mammalian cell types. The first convincing example of a spectrin-like molecule in nonerythroid cells was fodrin, which is composed of a 240 kDa (α) and 235 kDa (ß) subunit, identified in neuronal tissue (Levine and Willard, 1981). Another spectrin-like protein has been found in a wide variety of tissues. Genes for nonerythroid homologues of α and ß spectrin have also been described that encode proteins that are approximately 60% identical to their erythroid counterparts. The protein products of these genes may be altered by alternative processing of pre-mRNA, leading to even greater diversity of spectrin subunits (for review see Winkelmann and Forget, 1993). Spectrin-like proteins in nonerythroid cells are now generally called fodrin. In nonerythroid cells, functions that have been attributed to fodrin are known to include exocytosis of secretory

granules of chromaffin cells (Perrin and Aunis, 1985), regulation of receptor domains on plasma membranes (Bourguignon et al., 1985), and maintenance of epithelial cell polarity (Nelson and Veshnock, 1986).

Human erythrocyte protein 4.1 is a peripheral membrane phosphoprotein that migrates as two major polypeptides of 80 kDa and 78 kDa when analyzed on sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE). These two polypeptides, referred to as protein 4.1a and protein 4.1b, bind to spectrin with equal efficiency, promoting spectrin-actin interaction. Protein 4.1 binds with high affinity to glycophorin C (ß), an intrinsic membrane protein, serving as an anchoring site of the skeleton to the membrane and has been shown to bind to band 3, an anion exchange protein (Elliott and Ralston, 1984; Danilov et al., 1990). Protein 4.1 has been shown to be essential to maintain the stability of the erythrocyte membrane (Takakuwa et al., 1986). Several proteins immunologically related to protein 4.1 have been found in various nonerythroid tissues, including fibroblasts (Cohen et al., 1982), neurons (Goodman et al., 1984; Kanda et al., 1986; Tsumoto et al., 1988; Yorifuji et al., 1989), lens (Aster et al., 1984), endothelium (Leto et al., 1986); thyroid gland (Shimizu et al., 1992) and chromaffin cells (Burgoyne and Baines, 1987) as well as in several blood cells such as lymphocytes, polymorpho-nuclear leukocytes and platelets (Spiegel et al., 1984).

Erythrocyte adducin is characterized as a heterodimer with subunits of 97 kDa (α) and 103 kDa (ß) that can promote the association of spectrin with actin in a manner similar to that of protein 4.1 (Mische et al., 1987). Adducin has also been isolated from bovine brain membranes (Bennett et al., 1988), and isoforms of this protein have been detected in various tissues and cells, including lung (Bennett et al., 1988), kidney (Bennett et al., 1988), lens (Kaiser et al., 1989), Madin-Darby Canine Kidney (MDCK) cells (Pinto-Correia et al., 1991) and fibroblasts (Waasem and Palfrey, 1990).

Erythrocyte ankyrin (protein 2.1) is a globular and somewhat asymmetric protein of 210 kDa. In the erythrocytes, ankyrin binds to spectrin and band 3, maintaining the interaction between the membrane skeleton and lipid bilayer. Consequently, band 3, an anion-channel, is widely distributed on the whole surface of the erythrocytes (for review see Bennett, 1992). Proteins immunologically related to erythrocyte ankyrin have been detected in various nonerythroid tissues (Bennett and Davis, 1981; Drenckhahn and Bennett, 1987; Koob et al., 1987). In nonerythroid cells, ankyrin associates with a sodium-channel in neurons (Srinivasan et al., 1988; Kordeli et al., 1990), CD44 (GP85) in lymphoma cells (Bourguignon et al., 1986; Kalomiris and Bourguignon, 1988), and Na^+, K^+-ATPAse in the kidney (Morrow et al., 1989; Nelson and Hammerton, 1989; Koob et al., 1990) and in the choroid plexus (Alper et al., 1994). The association of ankyrin with these proteins suggests that ankyrin plays a role in transmitting signals between the inside and outside of the cells through its intramembranous structure. Until now, ankyrins isolated from erythrocytes and brain are the best characterized members of the family. Three ankyrin genes ($ankyrin_R$, $ankyrin_B$ and $ankyrin_G$) have been characterized from erythrocytes and brain (Lambert

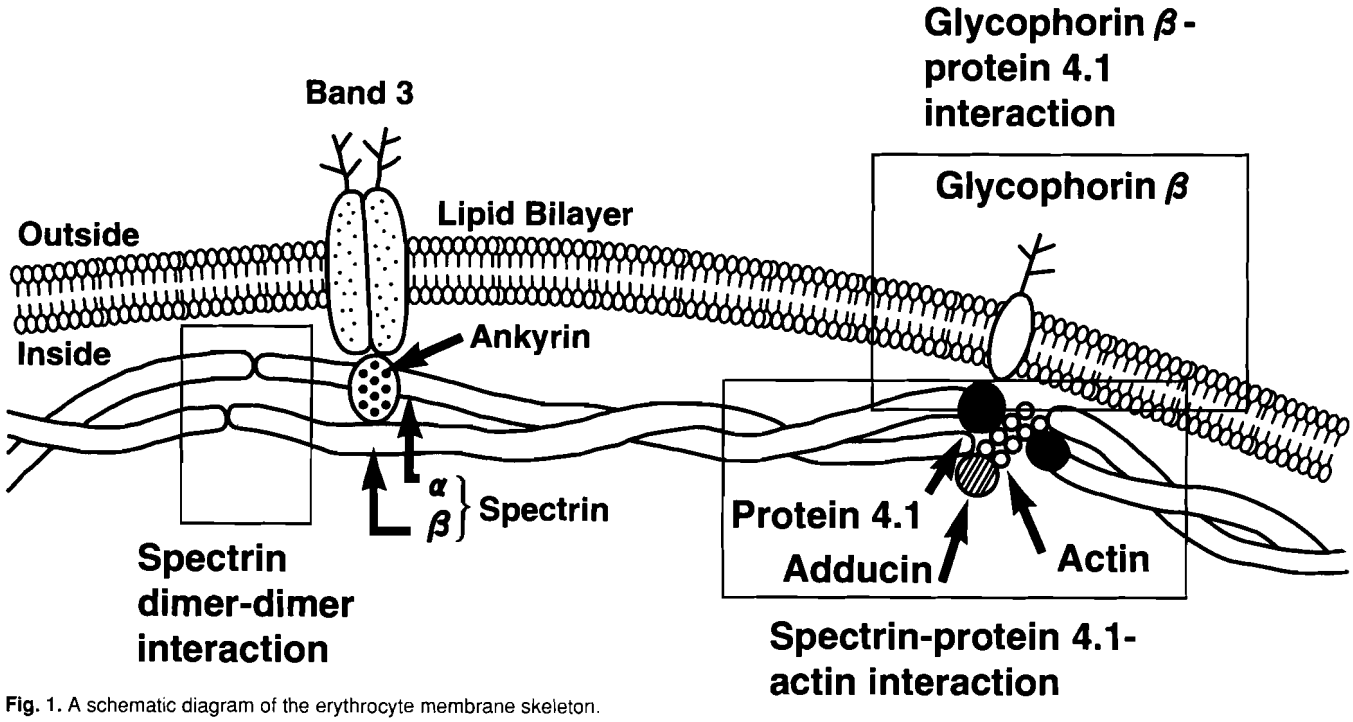

Fig. 1. A schematic diagram of the erythrocyte membrane skeleton.

and Bennett, 1993; Kordeli et al., 1995).

Other proteins, including protein 4.9 (syn. dematin) (Siegel and Branton, 1985) and tropomyosin (Fowler and Bennett, 1984) are also likely to participate in a membrane skeletal network. Immuno-analogues of protein 4.9 have also been studied in several tissues (Faquin et al., 1988).

Nonerythroid membrane skeletal proteins in human skin

The skin is an important barrier that protects the body from the damaging effects of the outside environment. As surface of the skin and lining cells in the epidermis, keratinocytes share a protective function in the skin. Keratinocyte proteins are involved in a wide variety of functions such as the cell-to-cell and cell-to-substratum adhesion, stratification, and maintenance of the cell shape. Over the course of differentiation, these functional properties may change, reflecting the expression of new or modified proteins. Some of these proteins are manifested by the production of an extensive cytoskeletal network of keratin filaments, actin filaments and microtubules.

Until recently, most of the research on membrane skeletal proteins has been carried out with erythrocytes and brain tissues. The findings that proteins cross-reactive with the erythrocyte peripheral membrane proteins exist in many nonerythroid cells support the idea that the immuno-analogues of erythrocyte membrane proteins are also present in human keratinocytes. Kariniemi et al. (1984) reported that the spectrin-like proteins are localized in the epidermis. They used antibodies against a 230-kDa polypeptide (p230) isolated from the calf lens, which cross-reacts with erythroid α-spectrin. These antibodies stain in the periphery of the human epidermal cells. Then, using antibodies against human erythrocyte spectrin, we studied the immuno-analogues of erythrocyte spectrin in epidermal keratinocytes (Shimizu et al., 1990). An immunohistochemical analysis found that spectrin was localized preferentially in the basal layer (Fig. 2a). Spectrin-like proteins in epidermis have also been studied with antibodies against brain fodrin by several groups (Kainer et al., 1989; Shimizu et al., 1990; Yoneda et al., 1990). Spectrin-like protein (fodrin) of keratinocytes is composed of subunits of 240 kDa (α) and 235 kDa (ß), which appear to be identical to the corresponding subunits of brain fodrin

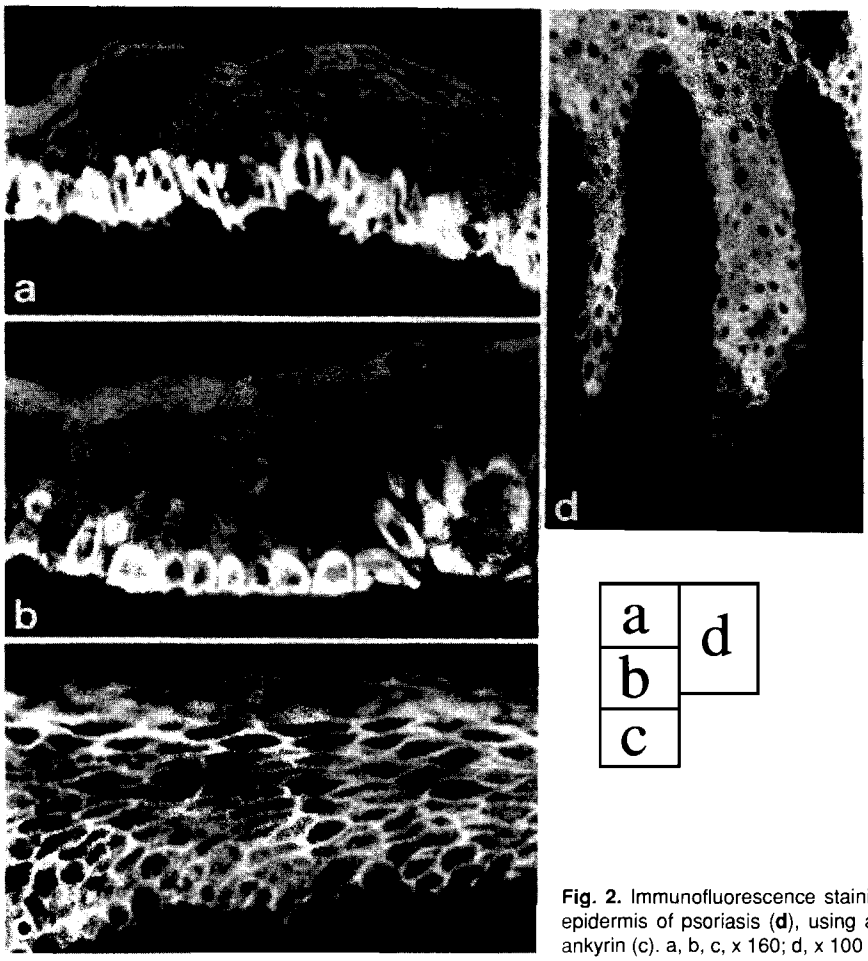

Fig. 2. Immunofluorescence staining of normal human epidermis (**a,b,c**), and lesional epidermis of psoriasis (**d**), using antibodies against spectrin (a), protein 4.1 (b,d) and ankyrin (c). a, b, c, x 160; d, x 100

(Shimizu et al., 1990).

Another membrane skeletal constituent, protein 4.1 immuno-analogues, has also been studied in the human epidermis. Analysis with immunofluorescence microscopy revealed that the plasma membrane of the basal cells was stained intensively, whereas spinous cells were moderately stained (Fig. 2b) (Shimizu et al., 1991). Immunoblot analysis revealed that the human epidermis contains 4.1-like proteins of 80 kDa, which have identical molecular mass to that of erythrocyte protein 4.1 (Shimizu et al., 1991). Mutha et al. (1991) were able to isolate cDNA clones of protein 4.1 from a human keratinocyte library. The sequence confirms the active transcription in keratinocytes of protein 4.1 genes.

Moreover, adducin was shown to be present in the epidermis by Kaiser et al. (1993). An immunochemical study found that adducin was localized at the cell periphery in the epidermis. Immunohistochemical analysis of the epidermis revealed an intense fluorescence in the basal layer, whereas the stratum spinosum showed moderate staining; these differential staining patterns were similar to those observed for spectrin and protein 4.1 in the epidermis described above. These proteins may have an initial role in assembly of cell junctions, but this role is lost after completion of these structures, as was suggested previously (Kaiser et al., 1989).

During analysis of the membrane skeleton in the epidermis, we recently demonstrated that the human epidermis also contains an ankyrin-like protein of 210 kDa (Shimizu et al., 1995b). The distribution of this ankyrin-like protein is different from that of spectrin (fodrin), protein 4.1, and adducin-like proteins in the human epidermis. Antibodies to ankyrin reacted with the peripheral cytoplasm of whole epidermal cell layers (Fig. 2c). On the other hand, in normal epidermis, cellular localizations of spectrin (fodrin), adducin, and protein 4.1-like protein(s) have been shown to vary with stage differentiation. The reasons for these staining differences of distribution are currently unknown.

The expression of membrane skeletal proteins in diseases

With an increased understanding of the structure and function of the erythrocyte membrane, several membrane protein mutations have been identified in hereditary disorders of the erythrocyte membrane (Palek and Sahr, 1992). In hereditary elliptocytosis (HE), many cases with a defective self-association of the spectrin dimer to a tetramer have been reported (Agre et al., 1982). Abnormality or deficiency of protein 4.1 has also been found in cases with HE (Tchernia et al., 1981; McGuire et al., 1988). These membranes have been shown to have decreased stability. These studies indicate that the membrane skeleton is essential for the normal survival of erythrocytes in the circulation and that defects in the skeletal proteins can be the basis for disease (Palek and Lambert, 1990). Abnormal erythroblasts. Friend erythroleukemia cells, have been shown to contain a protein 4.1 doublet and two minor bands of 105 kDa and 43 kDa that cross-react with anti-human protein 4.1 IgG (Benabdallah et al., 1991). Conboy et al. (1991) indicate that splicing switches may account for the considerable development-specific and tissue-specific heterogeneity in protein 4.1 expression by showing the abundance of alternative splicing events in erythroid 4.1 mRNAs. Recently, impressive evidence was reported by Rousseaux-Prévost et al. (1994) that, in spermatozoa of infertile patients with severely amorphous sperm heads, protein 4.1 has an abnormal subcellular localization and appears as high-molecular weight isoforms (135 kDa). From these observations, they assumed that the protein 4.1 transcript loses the upstream initiation codon by a stage-dependent alternative splicing in amorphous sperm heads.

As for skin diseases, psoriasis is a chronic skin disorder of widespread occurrence which is characterized by epidermal hyperplasia. Lesional epidermis shows a rapid turnover of keratinocytes and a defect in keratinization, the etiology and pathogenesis of which remain undetermined. Although it cannot be demonstrated that the epidermis is the site that is primarily affected in psoriasis, it is unquestionable that epidermal symptoms are very precocious during the development of skin lesions (Parent et al., 1990). Until recently, numerous studies have been performed to elucidate the mechanism of increased epidermal cell proliferation in psoriatic lesions. Recent immunochemical studies in our laboratory revealed a pronounced difference in protein 4.1 staining in the lesional epidermis of psoriatic skin compared to non-lesional epidermis (Shimizu et al., 1995a). Enhanced suprabasal cytoplasmic expression of a 45 kDa polypeptide was found in psoriatic keratinocytes, suggesting that this low molecular mass polypeptide might lack the ability to bind to the integral components of the membrane (Fig. 1d). Observations of differential expression and distribution of protein 4.1 in lesional epidermis of psoriasis indicate that alterations of this protein may be important in the pathogenesis of this disease.

Spectrin-like protein (fodrin) in nonerythroid cells is reported to participate in the establishment of cellular orientation and polarity (Molitoris and Nelson, 1990). Simpson and Page (1992) examined the localization of fodrin in epithelial proliferative disease of the breast. By immunohistochemical analysis, the polarized distribution of fodrin is lost in proliferative breast epithelium, compared to normal breast epithelium. Altered fodrin distribution in hyperplasia may correlate with the histological findings of the loss of cellular orientation and polarity. In psoriatic epidermis, fodrin distribution was found to be similar to that in normal epidermis (Shimizu et al., 1995a). The reason might be that epidermal structure is retained in psoriasis, unlike in neoplastic hyperplasia of keratinocytes.

Mahrle and Orfanos (1977) suggested that psoriasis

might involve an altered epidermal plasma membrane system. Since then, it has been hypothesized that membrane alterations may be part of a basic defect in psoriasis that may involve various tissues, including the skin. Kumar et al. (1983) reported that erythrocytes of psoriatic patients demonstrate altered membrane phosphorylation in vitro, a finding consistent with structural membrane abnormalities. The finding of decreased erythrocyte deformability in psoriasis patients, reported by Peserico et al. (1988), also suggests a structural or functional abnormality of the erythrocyte membrane in psoriasis. Based on these studies, one can speculate that psoriasis may affect cell membrane modifications not only in epidermal keratinocytes but also in erythrocytes.

Dynamics of localization and function of membrane skeletal proteins in keratinocytes

The current understanding of the function of membrane skeletal proteins in nonerythroid tissues including keratinocytes is incomplete. The proliferation and differentiation of cultured keratinocytes can be manipulated by changing Ca^{2+} concentrations in the culture medium (Ca^{2+} switch). This Ca^{2+} switch is considered to be a good model for studying the regulation of differentiation of the epidermal keratinocytes. Keratinocytes stratify and form the desmosome and adherence junction where they are cultured in medium with standard calcium (1.2-2.0 mM) (Hennings et al., 1980; Magee et al., 1987; O'Keefe et al., 1987). The Ca^{2+} switch induces a change in localization of actin filaments from the cytosol to the membrane (Magee et al., 1987; O'Keefe et al., 1987). The reorganization of other cytoskeletal components has also been observed during the differentiation of keratinocytes (Zamansky et al., 1991). Concerning the membrane skeletal proteins in keratinocytes, several experiments were performed *in vitro*. Kaiser et al. (1989) observed that adducin is localized diffusely in the cytoplasm in a low-Ca^{2+} medium, while adducin becomes concentrated at sites of the cell-cell contact due to an increase in the Ca^{2+} concentrations. Then, using a mouse keratinocyte cell line (Pam 212), fodrin localization was studied. Fodrin is present in the cytoplasm of the cells iN low concentrations of Ca^{2+}, but it is in the plasma membrane when cells are placed under standard concentrations of Ca^{2+} (Yoneda et al., 1990). Similar redistribution of protein 4.1 from the cytoplasm to the cell boundary was also demonstrated in our recent experiments (Shimizu, 1993). Since Ca^{2+} plays an important role in the regulation of the formation of cell-cell junctions, these studies suggest that membrane skeletal proteins such as fodrin, adducin and protein 4.1 analogues in cultured keratinocytes may regulate cell-cell interdigitations in response to changes in the Ca^{2+} concentrations in culture medium. Assembly of a membrane skeletal lattice at cell-cell contacts could increase mechanical stability of the membrane and provide a mechanism for immobilization of other membrane proteins involved in the construction of cell junctions (Kaiser et al., 1989). This dynamic organization of nonerythroid membrane skeletal proteins of keratinocytes is a distinct feature that erythrocytes do not have. The role of intracellular Ca^{2+} has been widely studied in erythrocytes. It has been proposed that elevated intracellular Ca^{2+} levels affect red cell shape, deformability, surface area, ion fluxes, proteolysis and cross-linking of membrane proteins (Turrini et al., 1985; Cohen and Gascard, 1992). In nonerythroid cells, the relationships of these membrane skeletal proteins to the regulation of cell-cell contacts were reported by several investigators. For example, in endothelial cells, protein 4.1 analogues localize in the perinuclear region; as a result of stimuli by components of the extracellular matrix and contact with other cells, protein 4.1 analogues translocated to the cell-cell contact sites (Leto et al,., 1986). Fodrin distribution was examined with MDCK cells by Nelson and Veshnock (1987). Significant changes in the biophysical and biochemical properties (Ca^{2+} switch) and cellular localization of fodrin have been observed during the development of cell polarity in MDCK cells. It is suggested that membrane skeletal proteins may play a role in establishing and maintaining membrane domains in differentiated cells (Nelson and Veshnock, 1987).

Comments

The functions of spectrin (fodrin), protein 4.1 and adducin analogues in nonerythroid cells are still unclear. In keratinocytes, these proteins may play a role in maintaining the polarity of membrane proteins by connecting them to the cytoskeleton, regulating cell-cell interdigitations and stabilizing newly synthesized cell membranes before elaboration of cell-cell interdigitations. Purification of these membrane proteins from the epidermis and the study of their interactions with other skeletal proteins and integral membrane proteins are needed to clarify the functions of these proteins in the skin. In neoplastic proliferative disorders, cellular polarity and orientation of keratinocytes are lost whereas epidermal structure is retained in psoriasis. Therefore, it is important to analyze the expression and distribution of these proteins in neoplastic skin diseases such as basal cell carcinoma and squamous cell carcinoma. Characterization of these proteins promises to yield information fundamental to an understanding of keratinocyte function in normal and disease states.

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