Keratinocytes Express the CD146 (Muc18/S-Endo) Antigen in Tissue Culture and During Inflammatory Skin Diseases

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The CD146 (or MUC18/MEL-CAM) antigen is a cell adhesion molecule of the immunoglobulin superfamily. Besides in melanoma, expression of CD146 antigen has been demonstrated in breast epithelia and hair follicles. We studied its expression by human keratinocytes in culture as well as in neoplastic and inflammatory skin diseases. Staining of primary cultured keratinocytes revealed expression of CD146 on the cell membrane, preferentially on cell-cell contact sites. Western blot analysis of keratinocytes detected a band of 113 kDa, corresponding to the CD146 protein. In contrast to primary keratinocytes, neither CD146 protein nor mRNA expression was found in the keratinocyte-derived cell lines A431 and HaCaT. Treatment of keratinocytes with the proinflammatory cytokines interleukin-1 and interleukin-6, tumor necrosis factor-α, and interferon-γ, resulted in no change of CD146 expression and incubation with phorbol 12-myristate 13-acetate led to a reduction of CD146 on keratinocytes. By contrast, when culturing keratinocytes in medium devoid of growth supplements, a distinct upregulation was observed as compared with culture in fully supplemented medium. In normal human epidermis expression of the CD146 antigen was not detectable. It was strongly upregulated, however, on suprabasal keratinocytes in psoriasis, in lichen planus, in the epidermis overlying skin neoplasms, and in viral warts. In squamous cell carcinomas and basal cell carcinomas only a minority of tumor cells expressed CD146. Our findings suggest that the CD146 antigen represents an activation marker of keratinocytes and may be involved in cutaneous inflammatory tissue reaction. Key words: adhesion/inflammation/psoriasis/skin cancer. J Invest Dermatol 115:219–224, 2000

The CD146 antigen, also known as MUC18, melanoma cell adhesion molecule (Mel-CAM) or S-Endo (Bardin et al, 1996) is a 113 kDa integral membrane glycoprotein belonging to the immunoglobulin superfamily (Lehmann et al, 1987; Johnson et al, 1996). It consists of an extracellular region with five immunoglobulin domains, a transmembrane stretch, and a short cytoplasmic tail with several potential phosphorylation sites (Lehmann et al, 1989). Structural and sequence analyses have revealed significant homologies with other known cell adhesion molecules, including BEN/SC-1/DM-GRASP (Burns et al, 1991; Tanaka et al, 1991; Pourquie et al, 1992) and gicerin (Taira et al, 1994) in the chicken, neuronin in goldfish (Paschke et al, 1992; Laessing et al, 1994), and N-CAM (Cunningham et al, 1987), and HEMCAM (Vainio et al, 1996) in humans. CD146 expression was found in melanoma cells, in the cerebellar cortex, in the intermediate trophoblast, on smooth muscle cells, activated T cells, vascular endothelial cells, and breast epithelium (Lehmann et al, 1987; Sers et al, 1994; Shih and Kurman, 1996; Pickl et al, 1997; Shih et al, 1997a). As an yet unidentified ligand for CD146, mediating heterophilic aggregation, has been proposed to be expressed on melanoma cells and endothelial cells (Johnson et al, 1996; Shih et al, 1997b). 

Studies concerning the function of CD146 have mainly focused on melanoma cells. Originally, CD146 was considered a melanoma progression marker, as normal melanocytes in the epidermis are negative for this antigen and more than 80% of primary human melanomas express it (Johnson et al, 1996). Transfection of CD146-negative melanoma cells with CD146 leads to increased homotypic adhesion, increased attachment to endothelial cells, and decreased ability to adhere to laminin (Xie et al, 1997). In nude mice, CD146 transfectants were highly tumorigenic and had a higher metastatic potential than control melanoma cells (Xie et al, 1997). As opposed to what has been observed for melanocytes and melanomas, CD146 is constitutively expressed by normal mammary epithelia and is downregulated in breast carcinomas (Shih et al, 1997a). CD146 transfection of breast cancer cells inhibited their growth in SCID mice, suggesting that CD146 may play a part in the suppression of breast carcinoma.

Expression of CD146 has been described in human hair follicles in the past (Lehmann et al, 1987; Shih et al, 1998), but little is known about its expression on keratinocytes (KC) in normal and...
diseased human skin. We therefore investigated CD146 expression in several inflammatory and neoplastic skin disorders and on cultured KC.

MATERIALS AND METHODS

Tissue samples and cell culture Tissue samples were derived from biopsies obtained for diagnostic or therapeutic purposes after informed consent by the patients. Samples included normal appearing perilesional skin of nevocellular nevi (n = 8), psoriasis (n = 8), lichen planus (n = 4), chronic cutaneous lupus erythematosus (n = 3), bullous pemphigoid (n = 3), viral warts (n = 6), Bowen’s disease (n = 4), keratoacanthomas (n = 2), basal cell carcinomas (n = 15), and squamous cell carcinomas of the skin (n = 5) and hypopharynx (n = 3). Human neonatal foreskin KC derived from three different donors were purchased from Clonetics (San Diego, CA). KC were cultured under low-Ca2+ conditions (0.15 mM) in serum-free KC growth medium (KGM, Clonetics), supplemented with human recombinant epidermal growth factor (0.1 ng/mL), bovine pituitary extract, insulin (5 µg per mL), hydrocortisone (0.5 µg per mL), and gentamicin/amphotericin B (50 µg per mL/50 µg per mL) at 37°C in 5% CO2. In some experiments the cells were cultured in medium without supplements (KGM basal medium, KBM). The epidermoid carcinoma cell line A431, the immortalized KC cell line HaCaT, and the melanoma cell lines SkMel28 and RHTP49 were grown under standard culture conditions in RPMI 1640 with 10% fetal bovine serum and 1% L-glutamine (GIBCO-BRL Life Technologies, Vienna, Austria).

Antibodies and cytokines The following mouse monoclonal antibodies (MoAb) against human MUC18/S-endo/CD146 were obtained from the VI Workshop of Leukocyte typing: E057, E058, E059, E065, E077, E078. Anti-pancytokeratin (LU-5) was purchased from DiaNova (Hamburg, Germany). Isotype-matched antibodies (IgG1, Coulter Immunology, Hialeah, FL) were used as negative control. The following cytokines and mediators were used: interferon-γ (Boehringer, Ingelheim, Germany), tumor necrosis factor-α (R&D Systems, Minneapolis, MN), interleukin (IL)–1 (Genzyme, Cambridge, UK), IL-6 (Gibco BRL Life Technologies), phorbol 12-myristate 13-acetate (PMA, Sigma, St Louis, MO).

Immunohistochemistry A standard streptavidin–peroxidase method was followed for immunohistochemistry (Weninger et al., 1998). In brief, cryostat sections were fixed in ice-cold acetone for 10 min. Endogenous peroxidase was blocked with methanol/1% H2O2. After incubation with 10% sheep serum/2% bovine serum albumin, the sections were exposed to the primary MoAb (1 µg per mL) for 1–2 h at room temperature, followed by biotinylated sheep anti-mouse F(ab)2 (Amersham, Little Chalfont, U.K.) and streptavidin–biotin complex (Dako, Glostrup, Denmark). Antibody binding was visualized using diaminobenzidine (Dako). Sections were counterstained with hematoxylin, dehydrated and mounted.

Immunofluorescence staining of cultured KC Staining of cultured KC was performed either directly on cells grown on LAB-TEC slides (Nalge Nunc International, Naperville, IL) in KBM or after trypsinization in a single cell suspension. After incubation of acetone–treated KC with the MoAb for 1 h, slides were overlayed with fluorescein isothiocyanate–labeled goat anti-mouse serum (1:100, An der Grub, Vienna, Austria). Immunofluorescence was evaluated using a confocal laser microscope (LSM 410, Zeiss, Oberkochen, Germany).

For studying cell surface expression of CD146, KC grown in T25 flasks (Costar, Cambridge, MA) were detached with trypsin. Suspended cells were incubated with MoAb E065 (1:1000) or an appropriate isotype-matched control antibody for 30 min at 4°C followed by a fluorescein isothiocyanate–goat anti-mouse serum (An der Grub). Cells were analyzed using a FACScan (Becton Dickinson, San Jose, CA). For some experiments, KC were grown in KBM or KGM overnight under low or high Ca2+ conditions. On the next day, medium was changed (either KBM or KGM) and various cytokines were added for another 24 or 48 h.

Western blot analysis For western blot analysis KC, A431 cells, HaCaT cells or SkMel28 cells were lysed in 1% NP40 buffer containing 0.2% sodium dodecyl sulfate (Weninger et al., 1998). After quantitation proteins were electrophoresed through an 8% polyacrylamide gel and transferred on to nitrocellulose membranes (BioRad, Hercules, CA). The membrane was sequentially incubated with MoAb E065 (1:100) and horseradish peroxidase–conjugated goat anti-mouse antibody (Amersham, 1:10000). Specific reaction was detected by chemiluminescence (ECL-kit, Amersham, Little Chalfont, U.K.) according to the manufacturer’s instructions. In some experiments equal loading was confirmed by Ponceau-S (Merck, Vienna, Austria) staining of the blots.

To detect CD146 shedded to the culture medium, glycoproteins were enriched from the total supernatant of KC cultured in T25 flasks for 48 h under subconfluent conditions. As described previously (Pammer et al., 1996) the supernatant was reacted to lentil–lectin beads (Lentil–lectin Sepharose 4B, Pharmacia, Uppsala, Sweden) and after several washes, glycoproteins were eluted from the beads in 70 µL of 1 mol per L 1-methyl-mannopyranoside (Sigma). The glycoprotein–enriched eluates were subsequently subjected to western blot analysis. As positive control for the purification procedure lysates of SkMel28 cells were added to the conditioned medium, which were then treated as described above.

Reverse transcriptase–polymerase chain reaction (reverse transcriptase–PCR) Total RNA from KC and the cell lines was prepared using a commercially available kit (RNAzol, CINNA/Biotecx, Houston, TX). cDNA was synthesized using superscript Rnase H–RT (GIBCO) and oligo–dT15 (Boehringer Mannheim) from 1 µg total RNA as described previously (Ballaun et al., 1995) and PCR was performed using CD146 specific primers as published by Hoon et al. (1995). Successful CD146 cDNA synthesis was confirmed by agarose gel electrophoresis. PCR products were separated by agarose gel electrophoresis, transferred on to a nylon membrane, and hybridized to an (α-32P) end–labeled oligonucleotide: 5’–GTCATATCTTCTCGTGTGGCCGGA3’, which is specific for CD146 (Hoon et al., 1995).

RESULTS

The CD146 protein and mRNA are constitutively expressed by KC in primary culture but not by KC–derived cell lines Immunofluorescence staining of KC grown on chamber slides revealed that CD146 was constitutively expressed on the cell membrane (Fig 1a). Staining was particularly prominent at cell–cell contact sites. The isotype–matched control antibody showed no reactivity (Fig 1b). By flow cytometry, membrane expression of CD146 was found on cultured primary KC (Fig 2a, thin line), but not on A431 and HaCaT cells (not shown). When the cells were grown in KBM instead of KGM for 48 h, a distinct upregulation of
Figure 2. Upregulation of CD146 on KC expression by growth factor withdrawal. KC and SkMel28 melanoma cells were analyzed for CD146 expression by flow cytometry. (a) KC cultured for 48 h in KGM (thin line) showed weak CD146 expression (mean channel of fluorescence (MCF): 192; isotype: dotted line, MCF: 150) which was increased when KC were cultured in KBM (bold line) without growth factors (MCF: 239; isotype: dashed line, MCF: 145). (b) A similar regulation was seen when SkMel28 cells were cultured for 48 h in medium without growth supplements (bold line, MCF: 531; isotype: dotted line, MCF: 133) compared to fully supplemented medium (thin line, MCF: 455; isotype: dotted line, MCF: 114). (c) Culture of KC 48 h in KBM plus PMA (thin line, MCF: 185; isotype: dotted line, MCF: 151) reduced CD146 expression compared to KBM alone (bold line, same as in part a).

CD146 expression was found (Fig 2a, bold line). The same effect was observed when SkMel28 melanoma cells were cultured in medium devoid of fetal bovine serum (Fig 2b, bold line), i.e., CD146 was upregulated as compared with culture in fully supplemented medium (Fig 2b, thin line). Incubation of KC in KBM with PMA for 48 h resulted in a downregulation of CD146 expression (Fig 2c, thin line) as compared with KBM (Fig 2c, bold line). When the KC were cultured either in KBM or KGM in the presence of several cytokines, including IL-1 (2 U per ml), IL-6 (100 U per ml), interferon-γ (500 U per ml), and tumor necrosis factor-α (100 ng per ml) for 24 and 48 h no reproducible effect on CD146 expression was observed (not shown). Also, culture both in KGM and KBM under low (0.15 mM) and high (1.5 mM) Ca²⁺ conditions resulted in no change of CD146 expression of KC (not shown).

Western blot analysis of KC lysates detected a band of approximately 113 kDa in three individual KC preparations (Fig 3a, lanes 4–6). This band corresponded to that observed in the melanoma cell line SkMel28 (Fig 3a, lane 1). In contrast, no CD146 protein was detectable in lysates of A431 cells and HaCaT cells (Fig 3a, lanes 2 and 3). Corresponding to what we observed by fluorescence-activated cell sorter analysis, culture of KC in KBM upregulated CD146 protein expression (Fig 3b, lane 3) as compared with KC cultured in KGM (Fig 3b, lane 2). Incubation of KC in KGM and KBM with PMA clearly decreased detectable CD146 protein levels (Fig 3b, lanes 4 and 5). When an isotype matched control antibody was used instead of the anti-CD146 antibody, no specific reaction was observed (not shown).

To investigate whether shedding of CD146 contributes to the differences observed in CD146 expression by KC under different culture conditions we searched for its presence in the culture supernatant. Western blot analysis of enriched glycoproteins revealed no anti-CD146 reactive moieties in the culture supernatant under different conditions indicating that KC do not shed detectable amounts of this molecule (not shown).

When we performed reverse transcriptase–PCR and Southern analysis of PCR products CD146 mRNA expression was readily detectable in KC preparations (Fig 4, upper panel: lanes 3 and 4). In contrast to primary KC, no CD146 mRNA was detectable in A431
cells and HaCaT cells (Fig 4, upper panel: lanes 1 and 2) whereas a clear expression was found in SkMel28 and RHTP49 melanoma cells (Fig 4, upper panel, lanes 5 and 6). Specificity of the PCR reaction was confirmed by Southern hybridization (Fig 4, lower panel).

**CD146 protein expression is absent from normal epidermis but is upregulated in inflammatory skin diseases**  In accordance with previous publications, immunohistochemical staining of normal human skin (n = 8) revealed expression of CD146 on vascular smooth muscle and endothelial cells within the dermis (Fig 5a, c, d arrows). In hair follicles, KC in the outer root sheath below the area of the sebaceous gland invariably showed strong membrane staining (Fig 5b, arrows). No staining was observed in the upper portion of hair follicles and on KC within the epidermis (Fig 5a, b). This was in sharp contrast to psoriasis where intense staining of suprabasal KC was found in all of eight samples analyzed (Fig 5c, d, Table I). A similar staining was also seen in lichen planus (n = 4), the epidermis overlying or next to skin neoplasms, including KC-derived tumors and Kaposi's sarcoma (not shown). No epidermal reactivity was observed in chronic cutaneous lupus erythematosus lesions (n = 3, Table I) and bullous pemphigoid (n = 3, Table I). No CD146 staining of cells of the inflammatory infiltrate was detectable. For most experiments MoAb E065 was used, but identical results were obtained using MoAb E057, E058, E059, and E078. Only MoAb E077 did not reveal positive staining.

**In contrast to melanoma, CD146 is variably expressed in epithelial tumors**  Expression of CD146 in epithelial skin tumors was rather heterogeneous. One of four lesions of Bowen's disease (Fig 6a) and none of two keratoacanthomas (not shown) showed anti-CD146 reactivity (Table I). Expression in basal cell carcinomas (n = 15) was variable (Table I). Weak to moderate staining was observed in 11 of 15 samples (Fig 6b). In several of these, singly dispersed cells within the tumor bulk were found to express CD146 (Fig 6b, arrows), whereas the major cell population was negative. Four of eight squamous cell carcinomas were negative for CD146, whereas in the remaining weak to moderate expression was detected in a subset of the tumor cells (Fig 6c). In contrast to the above tumors, KC in all of six viral warts strongly expressed CD146 (Table I).

**DISCUSSION**

In this study we report that CD146, a member of the immunoglobulin superfamily, is constitutively expressed by KC in tissue culture and is induced on epidermal KC during certain inflammatory skin diseases. When we studied CD146 expression in normal appearing skin, we could confirm that it is regularly expressed in the outer root sheath of hair follicles (Lehmann et al., 1987; Shih et al., 1998), whereas it was completely absent from interfollicular epidermal KC. By contrast, in psoriatic lesions and in lichen planus suprabasal KC were strongly positive for CD146. The fact that the epidermis in other inflammatory skin diseases, i.e., chronic cutaneous lupus erythematosus and bullous pemphigoid, was negative indicates that probably the hyperproliferative state of the epidermis is the cause for CD146 upregulation and not the infiltration of inflammatory cells. This conclusion is further supported by the finding that KC in viral warts were also distinctly positive for this antigen and that CD146 was upregulated in acanthotic epidermis adjacent to skin tumors.

In contrast to KC in normal epidermis, cultured KC constitutively expressed CD146. As CD146 is induced on KC during hyperproliferation of the epidermis, one possible mechanism could be the stimulation of KC by a soluble factor.

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**Figure 4. Detection of CD146 mRNA transcripts in cultured KC by reverse transcriptase–PCR.** Upper panel: total RNA was extracted from cultured cells and cDNA was synthesized. PCR amplification products were subjected to agarose gel electrophoresis. Cells analyzed were: A431 cells (lane 1), HaCaT cells (lane 2), two different preparations of foreskin KC (lanes 3 and 4), SkMel28 (lane 5), and RHTP49 melanoma cells (lane 6). Lane 7, H2O control. Lower panel: Southern hybridization of the agarose gel shown in the upper panel using a CD146-specific [α-32P]-labeled oligonucleotide probe.

**Figure 5. Expression of CD146 in normal human skin and in psoriasis.** Immunohistochemical staining was performed on cryostat sections using an anti-CD146 monoclonal antibody. (a) Normal adult skin. No staining of interfollicular epidermal KC is observed in normal adult skin. Vascular smooth muscle cells (arrows) served as an internal positive control. (b) Distinct CD146 expression is detectable on cells in the outer root sheath of the hair follicle in the portion below the area of the sebaceous gland (arrows). (c, d) In psoriasis suprabasal KC show distinct membrane staining for CD146. Scale bar (a, c) 50 μm; (b, d) 25 μm.
Table I. CD146 staining of KC in inflammatory skin diseases and epidermal tumors

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<td>Viral warts</td>
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<sup>a</sup>Plus, weak; ++, moderate; ++++, strong staining.
<sup>b</sup>Proportion of stained cells: +, < 20%; ++, 20–50%; ++++, 50–80%.
<sup>c</sup>CCLE, chronic cutaneous lupus erythematosus; SCC, squamous cell carcinoma; BCC, basal cell carcinoma.

Figure 6. Expression of CD146 in Bowen’s disease, basal cell carcinomas, and squamous cell carcinomas. Immunohistochemical staining for CD146 was performed on cryostat section of (a) Bowen’s disease (arrow mark the border between normal epidermis and the CD146 negative lesion) and (b) basal cell carcinoma. Singly positive cells are visible within the tumor nodules (arrowheads). (c) A squamous cell carcinoma. For (d) serial section to c was stained with a pan-cytokeratin antibody. Scale bar: 25 μm.

The fact the CD146 expression by KC is enhanced at sites of cell to cell contact in conventional KC cultures suggests a role of this antigen in cell to cell adhesion. Indeed, there is strong experimental evidence that CD146 plays a part in cell adhesion (Johnson et al., 1996). It has been shown that CD146-positive melanoma cells show increased homotypic adhesion and adhere more efficiently to endothelial cells, but less efficiently to laminin (Xie et al., 1997). CD146 mediated adhesion has been suggested also to occur in a heterotypic manner (Shih et al., 1997b). Shih et al. (1997b) recently demonstrated that CD146-negative melanoma cells cluster with CD146-transfected U937 cells but not with control transfectants. They also adhere to CD146-positive endothelial cells and to nitrocellulose-bound CD146 protein (Shih et al., 1997b); however, a ligand for CD146 has not been characterized so far. Neoexpression of cell adhesion molecules during inflammatory skin diseases is a well known phenomenon. For example, ICAM-1, another member of the immunoglobulin superfamily, is upregulated on basal KC in psoriasis and other inflammatory dermatoses (Singer et al., 1989). Although the definitive function of ICAM-1 expression by KC is not known, it serves as a homing receptor for cells expressing its ligand, LFA-1, e.g., activated T cells (Dustin et al., 1988). In analogy to ICAM-1 one may speculate that CD146 could also mediate homing of leukocytes to suprabasal epidermal...
layers in psoriasis. To date, however, we have no data showing that CD146 expression by KC also has adhesive functions.

In contrast to viral warts CD146 expression was variable in other epithelial tumors. When we studied Bowen’s disease, basal cell carcinomas, and squamous cell carcinomas it was detectable in more than 50% of the samples, but was always restricted to a minor subpopulation of tumor cells. Within basal cell carcinomas in addition to tumor cells, numerous singly dispersed cells with dendritic morphology showed anti-CD146 staining. Further characterization of these cells revealed that they belonged to the melanocyte lineage (Weninger et al, manuscript in preparation).

The heterogeneous and sporadic expression of CD146 in epithelial tumors contrasts to its presence in melanoma where the majority of tumor cells are positive for this antigen (Lehmann et al, 1989). The pattern of CD146 expression in epidermal neoplasms prompts the question as to whether some of the tumor cells acquire the capacity to express this antigen, or whether malignant transformation of KC is paralleled by a reduced potential of tumor cells to express it. Although we cannot answer these questions from the present data, there are some indications which support the latter possibility: (i) the KC-derived cell lines A431 and HaCaT, which may be regarded as model cells for transformed KC, were consistently negative for CD146 at both the mRNA and protein level, and (ii) epidermal KC overlying skin tumors frequently expressed CD146 even when tumor cells were CD146 negative, indicating a subordinate role of the microenvironment on CD146 expression.

Reduced expression of intercellular adhesion molecules has been shown to facilitate invasion of cells into tissues. For example, loss of functional E-cadherin expression is thought to promote invasion of transformed epithelial cells (Birchmeier et al, 1993) and loss of E-cadherin expression was noted in several carcinomas, including epidermal nonmelanoma tumors in situ (Fuller et al, 1996). Interestingly, in a recent report Shih et al (1997a) demonstrated that CD146-transfected breast carcinoma cells established smaller tumors in SCID mice as compared with control transfectants, and that these tumors were more cohesive and less infiltrative than controls. They concluded that CD146 could act as a tumor suppressor in breast epithelium. As in contrast to epidermis, however, which is negative for this antigen under normal conditions, CD146 is constitutively expressed in breast epithelium, these tissues cannot be directly compared. Whether CD146 expression is able to suppress tumor invasion in the skin remains to be determined.

In summary we show that KC in primary culture express CD146 constitutively and that this antigen is upregulated on suprabasal KC during inflammatory skin diseases, e.g., psoriasis. We conclude that CD146 expression by KC may play a part in the pathophysiology of inflammatory skin diseases.

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