Human Desmocollin 1 (Dsc1) Is an Autoantigen for the Subcorneal Pustular Dermatosis Type of IgA Pemphigus

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IgA pemphigus showing IgA anti-keratinocyte cell surface autoantibodies is divided into subcorneal pustular dermatosis (SPD) and intraepidermal neutrophilic IgA dermatosis (IEN) types. We previously showed by immunoblotting that IgA from some IgA pemphigus patients reacted with bovine desmocollins (Dsc), but not human Dsc. To determine the antigen for IgA pemphigus, we focused on conformation-dependent epitopes of Dsc, because sera of patients with classical pemphigus recognize conformation-sensitive epitopes of desmogleins. We constructed mammalian expression vectors containing the entire coding sequences of human Dsc1, Dsc2, and Dsc3 and transiently transfected them into COS7 cells by lipofection. Immunofluorescence of COS7 cells transfected with single human Dscs showed that IgA antibodies of all six SPD-type IgA pemphigus cases reacted with the surface of cells expressing Dsc1, but not with cells expressing Dsc2 or Dsc3. In contrast, none of seven IEN-type IgA pemphigus cases reacted with cells transfected with any Dscs. These results convincingly indicate that human Dsc1 is an autoantigen for SPD-type IgA pemphigus, suggesting the possibility of an important role for Dsc1 in the pathogenesis of this disease. This study shows that a Dsc can be an autoimmune target in human skin disease. *Key words: autoimmune bullous disease/desmosome/keratinocyte/mammalian cell transfection. J Invest Dermatol 109:127–131, 1997*

Desmosomal cadherins are of two types, desmoglein (Dsg) and desmocollin (Dsc), both of which occur as three isoforms, Dsg1, 2, and 3 and Dsc1, 2, and 3, derived from different genes (Buxton et al, 1993; Amagai et al, 1995). Each Dsc gene produces two alternatively spliced products, the longer "a" form and the shorter "b" form, i.e., Dsc1a and Dsc1b.

Classical pemphigus, characterized by the presence of IgG anti-keratinocyte cell surface autoantibodies in the sera, consists of two major subtypes, pemphigus vulgaris (PV) and pemphigus foliaceus (PF). Brazilian PF is endemic in South America and shows features similar to PF. Extensive studies of these diseases have revealed that the autoantigen for PF and Brazilian PF is Dsg1 (Stanley et al, 1986; Hashimoto et al, 1990; Koch et al, 1990; Amagai et al, 1995) and for PV is Dsg3 (Hashimoto et al, 1990, Stanley et al, 1982; Amagai et al, 1991). Recently, a number of cases with anti-cell surface antibodies of the IgA class and showing distinct clinical features have been reported (Ebihara et al, 1991; Iwatsuki et al, 1991). Although

various terms have been used for these conditions, we will use the most simple term, IgA pemphigus, throughout this report. IgA pemphigus is divided into two subtypes, intraepidermal neutrophilic IgA dermatosis (IEN) type, showing pustule formation through the entire depth of the epidermis (Huff et al, 1985; Teraki et al, 1991), and subcorneal pustular dermatosis (SPD) type, showing pustules in the upper epidermis (Tagami et al, 1983, Hashimoto et al, 1987).

We have sought the target antigens for the IgA anti-keratinocyte cell surface autoantibodies of IgA pemphigus and found that certain IgA pemphigus sera recognized bovine Dsc (Ebihara et al, 1991; Iwatsuki et al, 1991). The significance of this finding, however, was unclear, because no IgA pemphigus sera reacted human Dsc by immunoblotting. We speculated that the cause of this failure may be that the IgA pemphigus sera react with conformation-dependent epitopes on Dsc because most pathogenic autoantibodies recognize conformation-sensitive epitopes of desmogleins in PV and PF (Amagai et al, 1994, 1995; Emery et al, 1995). The widely used technique of immunoprecipitation is able to detect such conformation-dependent epitopes on IgG antibodies. A technique for immunoprecipitation with IgA antibodies, however, has not been established.

In the current study, to detect antibodies to native Dsc molecules, we constructed mammalian expression vectors containing the entire coding sequence of human Dsc1, Dsc2, or Dsc3 and transfected them into COS7 cells by lipofection. We found that IgA in the sera of SPD type, but not IEN type, reacted with Dsc1. This study shows that human Dsc can be a target autoantigen in human

Figure 1. Clinical and histopathologic features are distinct between SPD and IEN types of IgA pemphigus. A patient of SPD type IgA pemphigus clinically showed superficial pustules (*a*). A patient of IEN type showed different cutaneous lesions with deeper pustules (*b*). A patient of SPD type histopathologically showed subcorneal pustule formation (*c*). A patient of IEN type showed pustule formation in the entire epidermis (*d*). *Scale bar*, 30 μm.
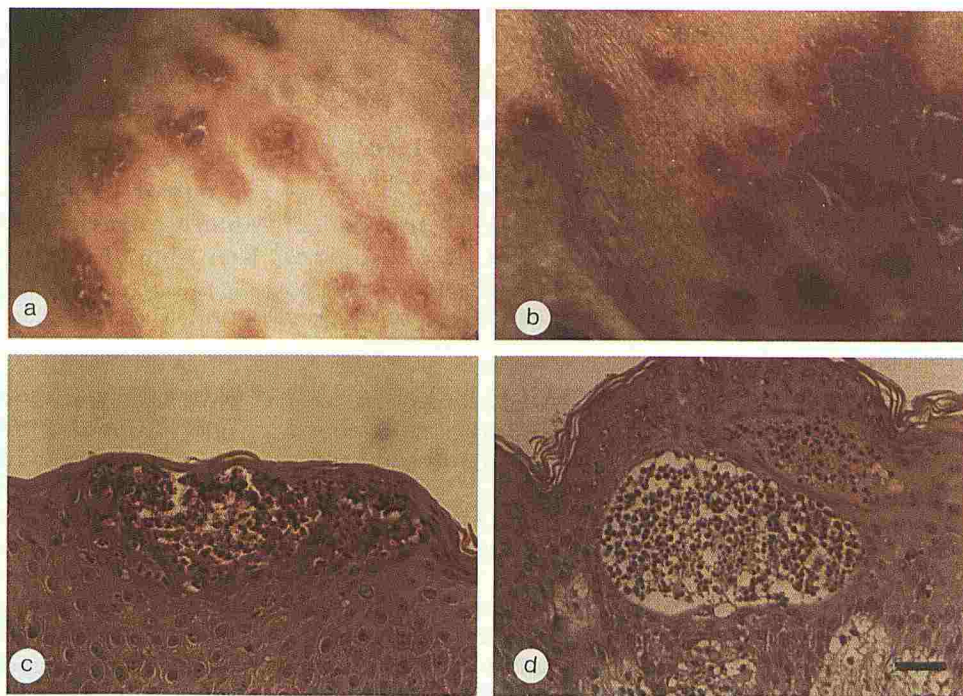
skin disease and also suggests an important insight into the pathogenesis of IgA pemphigus.

MATERIALS AND METHODS

Sera We selected 13 typical cases with IgA pemphigus (six SPD type and seven IEN type). All the patients of SPD type showed SPD-like clinical features of superficial pustules (**Fig 1*a***) and histopathologically subcorneal pustule formation in the upper epidermis (**Fig 1*c***). In contrast, all the patients of IEN type showed deeper vesiculo-pustular skin lesions, occasionally characterized by sunflower-like arrangement (**Fig 1*b***), and pustule formation in the entire epidermis (**Fig 1*d***).

Sera obtained from three patients each with PV and PF as well as from five normal volunteers were used as controls. All sera were stored at −30°C or −80°C as aliquots and used immediately after thawing because IgA may be less stable than IgG.

Antibodies Anti-Dsg monoclonal antibody (mAb) 32–2B (Vilela *et al*, 1987) and anti-Dsc mAb 52–3D (Collins *et al*, 1991) were characterized previously. Polyclonal antibody (pAb) JCMC was obtained by immunizing a rabbit with a recombinant bovine Dsc1-specific peptide (North *et al*, 1996). pAbs D1K2 and C+DGII were obtained by immunizing rabbits with peptides specific to human Dsc1 and Dsc2, respectively (Suzuki *et al*, manuscript in preparation).

Kawamura *et al* (1994) have recently isolated a novel human Dsc cDNA, which was tentatively designated human Dsc4. By comparison of human Dsc sequences with bovine Dsc sequences that are taken as standards (Collins *et al*, 1991; Parker *et al*, 1992; King *et al*, 1993; Theis *et al*, 1993; Troyanovsky *et al*, 1993; Kawamura *et al*, 1994; Legan *et al*, 1994; Yue *et al*, 1995), this is now re-designated human Dsc3. pAb LNCF3 was obtained by immunizing a rabbit with a human Dsc3-specific peptide (Suzuki *et al*, manuscript in preparation). The pAbs D1K2, C+DGII, and LNCF3 were generous gifts from Tadaaki Suzuki, Kazuo Kawamura, and Susumu Tsurufuji (Institute of Cytosignal Research, Inc.).

Preparation of Mammalian Cell Expression Constructs of Human Dsc1, 2, and 3 and Transfection into COS7 Cells To prepare a construct of human Dsc1, we used cDNA clones K24 (King *et al*, 1993) and K55 (King, 1994) (generous gifts from Dr. R.S. Buxton and Dr. I.A. King, Laboratory of Eukaryotic Molecular Genetics, National Institute for Medical Research, Mill Hill, London, U.K.). K24 contains almost the entire coding sequence except for the N-terminal end, and K55 contains the N-terminal region including the ATG initiation codon. To obtain cDNA covering the entire coding sequence, we utilized the *Acc*I sites at nucleotide 1494 in human Dsc1 and within the multiple cloning site of pBluescript II SK⁻. The 3.0-kbp fragment excised from K24 by *Acc*I digestion, which contains the C-terminal region of Dsc1, was subcloned into *Acc*I-digested K55, and a

clone with the proper orientation, designated K24/K55, was selected. The *Bam*HI/*Xba*I-digested fragment of K24/K55 containing the entire coding sequence of human Dsc1 was subcloned into the eukaryotic expression vector pcDNAI/Amp (Invitrogen Corp., San Diego, CA) previously digested with *Bam*HI/*Xba*I. A clone designated pcDNAI-hDsc1 was selected and propagated.

To prepare a construct of human Dsc2, the entire coding sequence was obtain by *Eco*RI digestion from pPB192 (a generous gift from Dr. R.S. Buxton and Dr. I.A. King), which is a pBluescript vector carrying the L5 clone (Parker *et al*, 1992). This cDNA fragment was subcloned into *Eco*RI-digested pcDNAI/Amp, and a clone with the proper orientation, designated pcDNAI-hDsc2, was selected.

pcDNAI-hDsc1 and pcDNAI-hDsc2 allow the expression of full-length cDNA inserts of human Dsc1 and Dsc2 under the control of the cytomegalovirus promoter.

Preparation of human Dsc3 cDNA (a generous gift from Tadaaki Suzuki, Kazuo Kawamura, and Susumu Tsurufuji) subcloned into the eukaryotic expression vector, pcDL-SRa296, was previously described (Kawamura *et al*, 1994). This clone allows the expression of a full-length human Dsc3 cDNA insert under the control of the simian virus early promoter, SRa (Kawamura *et al*, 1994; Takebe *et al*, 1988). All three clones produced "a" form (longer form) of each Dsc species.

Transient transfection of COS7 cells using lipofectAMIN reagent (Life Technologies, Gaithersburg, MD) was carried out according to the manufacturer's recommendations.

Immunofluorescence Immunofluorescence of normal human skin sections was performed by a standard method (Beutner *et al*, 1968) using fluorescein-conjugated anti-human IgG (specific to γ-chains), anti-human IgA (specific to α-chains), anti-mouse Igs, and anti-rabbit Igs antisera (DAKO, Glostrup, Denmark) as secondary antibodies.

Immunofluorescence of unfixed COS7 cells transiently transfected with Dsc1, 2, or 3 cDNAs was performed by the method of Stanley *et al* (1982). The cells cultured on coverglasses were first incubated at 4°C for 30 min in phosphate-buffered saline containing 1% bovine serum albumin and 0.1% NaN₃ to reduce background and membrane fluidity, respectively. The cells were incubated for 1 h at 4°C with patients' sera or specific antibodies diluted in the same buffer and subsequently with second antibodies conjugated with either FITC or rhodamine. For double labeling, the cells were incubated with a mixture of patients' sera and rabbit anti-Dsc pAb and subsequently with mixture of fluorescein-conjugated anti-human IgA antiserum and rhodamine-conjugated anti-rabbit Ig antiserum (DAKO). In some experiments, the cells were fixed and permeabilized by treatment with 100% methanol for 20 min at −20°C before immunostaining.
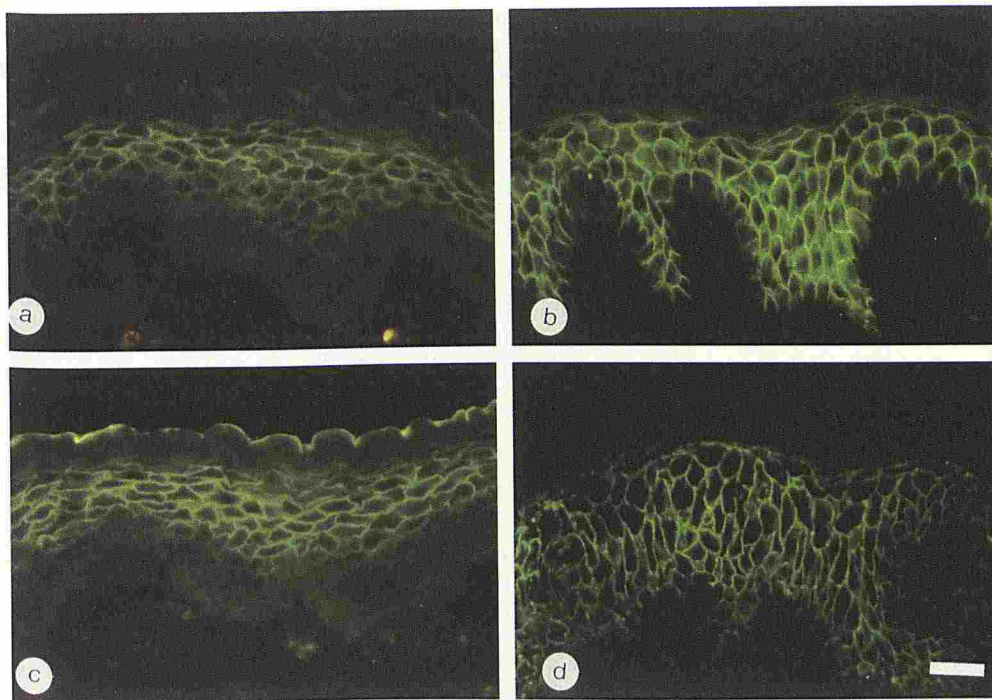
Figure 2. Immunofluorescence of normal human skin sections for anti-Dsc pAbs and IgA pemphigus sera suggested that SPD and IEN types may react with Dsc1 and Dsc3, respectively. Anti-Dsc1 peptide pAb JCMC stained keratinocyte cell surfaces in the upper epidermis (a), whereas anti-Dsc3 peptide pAb LNCF3 stained cell surfaces in the entire epidermis (b). A SPD type IgA pemphigus serum stained the uppermost epidermis (c), and an IEN type IgA pemphigus serum stained the entire epidermis (d). Scale bar, 30 μm.

Immunoblot Analysis of Normal Human Epidermal Extracts, Bovine Desmosome Preparations, and Extracts of COS7 Cells Transfected with Dsc1, 2, and 3 Preparation of extracts of normal human epidermis separated by dispase treatment, partial purification of desmosomes from bovine snout epidermis, and procedures for electrophoresis and immunoblotting were described previously (Hashimoto et al, 1990; Ebihara et al, 1991). All peroxidase-conjugated anti-human IgG (specific to γ-chains), anti-human IgA (specific to α-chains), anti-mouse Igs, and anti-rabbit Ig antisera used as secondary antibodies were obtained from DAKO.

COS7 cells transiently expressing Dsc1, 2, and 3 were lysed with Laemmli's sample buffer (Laemmli, 1970) and subjected to electrophoresis. Immunoblotting was performed by the same method as for epidermal extracts or desmosome preparations.

RESULTS

Immunofluorescence of Normal Human Skin Sections Suggested that SPD and IEN Types of IgA Pemphigus May React with Dsc1 and Dsc3, Respectively With immunofluorescence of normal human skin sections, anti-Dsc1 peptide pAbs (JCMC and D1K2) stained keratinocyte cell surfaces in the upper epidermis but not the keratinized layer (Fig 2a). By contrast, pAb against Dsc3 peptides (LNCF3) stained cell surfaces at all levels in the epidermis except the keratinized layer (Fig 2b). The reactivity of the anti-Dsc2 pAb C+DGII was very weak and stained cell surfaces of the spinous layer nearly down to the basal layer in normal skin, staining in the upper layers being much stronger. All
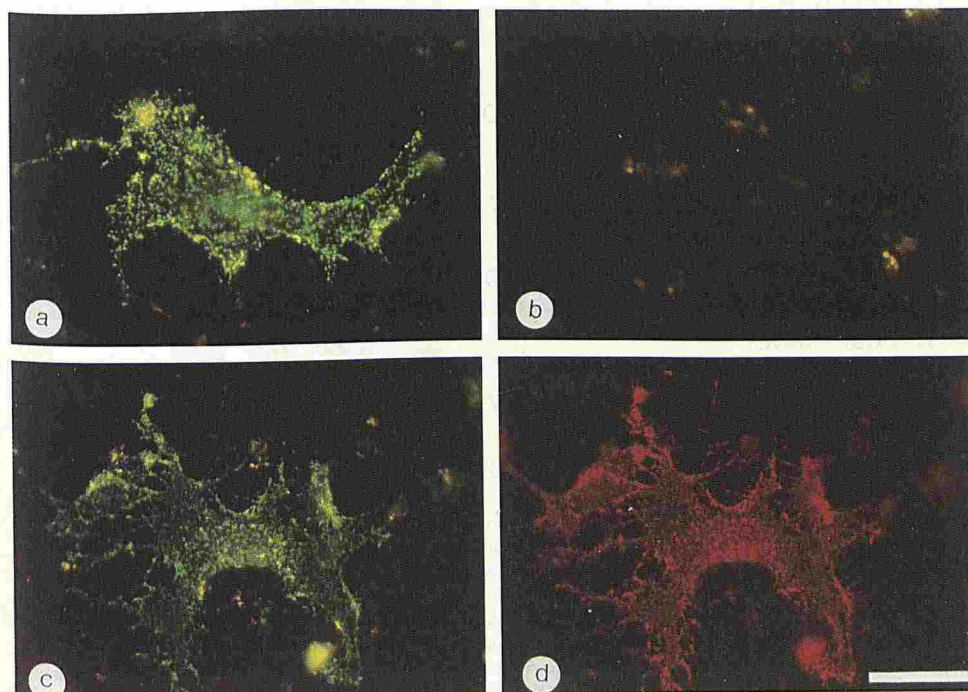
Figure 3. Immunofluorescence of COS7 cells transfected with human Dsc1, 2, or 3 indicated that the autoantigen for SPD type IgA pemphigus is Dsc1. A SPD type IgA pemphigus serum clearly stained cell surface of COS7 cells transfected with Dsc1 in a granular pattern (a), whereas an IEN type IgA pemphigus serum showed no reactivity (b). With double immunostaining, IgA antibodies in a SPD type of IgA pemphigus serum (c) and anti-Dsc1 pAb JCMC (d) showed exactly the same staining pattern. Scale bar, 30 μm.

Table I. Immunofluorescence of Various Antibodies and Sera with Normal Epidermal Sections and Dsc1-3-Transfected COS7 cells

Antibodies and Sera	(No.)	Section of Epidermis	COS7 Cells with		
			Dsc1	Dsc2	Dsc3
mAB 52-3D		(+) all layers	+	+	+
pAb JCMC		(+) upper layers	+	−	−
pAb D1K2		(+) upper layers	+	−	−
pAb C+DGII		(+) upper-mid layers	−	+	−
pAb LNCF3		(+) all layers	−	−	+
SPD type IgA pemphigus	(6)	(+) upper layers	6	0	0
IEN type IgA pemphigus	(7)	(+) all layers	0	0	0
PV	(3)	(+) lower layers	0	0	0
PF	(3)	(+) all layers	0	0	0
Normal	(5)	(−)	0	0	0

the sera of patients with SPD-type IgA pemphigus stained the upper epidermis (**Fig 2c**), resembling the pattern for Dsc1, whereas all the sera from patients with IEN-type IgA pemphigus stained the entire epidermis (**Fig 2d**), resembling staining for Dsc3. All the IgA pemphigus sera contained autoantibodies of IgA class, but not IgG class. All the results are summarized in **Table I**.

Immunoblotting of Epidermal Extracts and Desmosome Preparations Showed Controversial Results We first examined the reactivity of anti-Dsc autoantibodies of the IgA class by immunoblot analyses using both normal human epidermal extracts and bovine snout desmosome preparations and then compared their reactivities with those of anti-Dsc mAb or pAbs.

With immunoblotting of bovine desmosome preparations, the anti-Dsc mAb, 52–3D, and the rabbit pAbs against Dsc1, 2, and 3 peptides reacted with two protein bands of approximately 115 kDa and 105 kDa (data not shown, but see Ebihara *et al*, 1991). The IgA antibodies in the sera of three cases with SPD type and two cases with IEN type also reacted with a doublet of proteins showing similar mobilities to those recognized by the anti-Dsc antibodies. With immunoblotting of normal human epidermal extracts, none of the IgA pemphigus sera showed specific reactivity, whereas PV and PF sera reacted with the 130-kDa Dsg3 and the 160-kDa Dsg1 polypeptides, respectively, both of which were also recognized by the 32–2B anti-Dsg mAb. The 110-kDa and 100-kDa human Dscs were recognized by the 52–3D mAb (data not shown). The normal control sera showed no specific reactivity with immunoblotting of either antigen source.

Immunofluorescence of COS7 Cells Transfected with Human Dsc1, 2, or 3 Indicated That the Autoantigen for SPD-type IgA Pemphigus Is Dsc1 When COS7 cells transiently transfected with human Dsc1, 2, and 3 cDNAs were stained without fixation, the transfected cells reacted with pAbs specific to each Dsc: i.e., Dsc1 with JCMC and D1K2 pAbs, Dsc2 with C+DGII, and Dsc3 with LNCF3. No cross-reactivity was observed (data not shown). The positive cells, approximately 10% of the population, showed clear granular staining on the cell surface. Because 52–3D mAb reacts with the cytoplasmic domain of Dscs, the cells were permeabilized by treatment with 100% methanol. This mAb reacted with COS7 cells transfected with each of the three Dscs.

The IgA antibodies in all six sera of SPD-type IgA pemphigus reacted with COS7 cells expressing Dsc1 (**Fig 3a**), but none of the seven sera of the IEN type showed this reactivity (**Fig 3b**). The IgA antibodies in both types of IgA pemphigus did not react with either Dsc2 or Dsc3. IgG antibodies in three serum samples of SPD-type IgA pemphigus were examined, but no staining was observed in the Dsc-transfected cells. Neither IgG nor IgA in any control PV, PF,

or normal sera showed reactivity. All the results are summarized in **Table I**.

When the COS7 cells were stained simultaneously with SPD-type IgA pemphigus serum and anti-Dsc1 pAb JCMC, the cells stained with the patient's IgA were also stained with the pAb (**Fig 3c,d**). The staining intensity of both the IgA pemphigus sera and anti-Dsc1 pAb, however, was considerably reduced, suggesting that the patient's IgA reacts with a region similar to that recognized by the pAb and interferes with the reactivity of the pAb by steric hindrance.

To examine the possibility that IgA of IEN-type IgA pemphigus may react with intracytoplasmic domain of Dsc3, the cells permeabilized by 100% methanol treatment were also examined. None of the seven IEN-type IgA pemphigus sera, however, stained cell surfaces of Dsc3-transfected COS7 cells, although considerable background staining made the staining a little obscure (data not shown).

Immunoblotting of Lysates of COS7 Cells Transfected with Human Dsc1, 2, or 3 Confirmed That All the Dsc1–3 cDNA Clones Expressed Each Molecule with a Proper Size With immunoblotting of the lysate of COS7 cells transfected with human Dsc1, 2, or 3 cDNAs, proteins of approximately 100 kDa were detected by pAb specific for each Dsc. In **Fig 4**, *lane 1* is for standard molecular weight markers. *Lane 2* shows the lysate of Dsc1-transfected cells stained with anti-Dsc1 pAb JCMC; *lane 3* shows the lysate of Dsc2-transfected cells stained with pAb C+DGII, and *lane 4* shows the lysate of Dsc3-transfected cells stained with mAb 52–3D. The pAb LNCF3 reacted with the same protein band in the Dsc3-transfected cell lysate. No Dsc protein was detected by pAb specific to other isoforms of Dsc, confirming the specificity of each pAb. Whereas a single protein band was recognized in Dsc2- and Dsc3-transfected COS7 cells, however, a doublet of protein bands as well as lower protein bands was detected in Dsc1-transfected cells (*lane 2*). The reason for this reactivity is not known. These protein bands could be accounted for by unprocessed precursor or breakdown product. It is not likely that these bands represent "a" and "b" forms of Dsc, because the cells were transfected with cDNA. The same proteins were also recognized by the 52–3D mAb (data not shown). The Dscs expressed in COS7 cells, however, were not detected by IgA antibodies in any IgA pemphigus sera (data not shown).
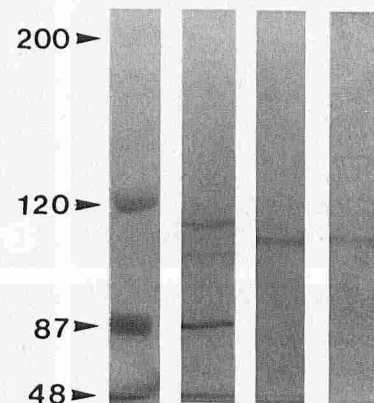
Figure 4. Immunoblotting of lysates of COS7 cells transiently transfected with human Dsc1, 2, or 3 confirmed that all the Dsc1–3 cDNA clones expressed each molecule with correct size. *Lane 1* is for standard molecular mass markers, indicating the positions of 200 kDa, 120 kDa, 87 kDa, and 48 kDa from top to bottom. *Lane 2* shows the lysate of Dsc1-transfected cells stained with anti-Dsc1 pAb JCMC; *lane 3* shows the lysate of a Dsc2-transfected cells stained with pAb C+DGII; and *lane 4* shows the lysate of a Dsc3-transfected cells stained with mAb 52–3D.

DISCUSSION

Immunofluorescence of normal human skin sections showed that IgA antibodies in sera of IEN-type IgA pemphigus bind to the keratinocyte cell surfaces at all levels in the epidermis, whereas IgA in sera of SPD-type IgA pemphigus bind only to the upper epidermis. The staining pattern of the SPD-type sera was very similar or identical to that shown by anti-Dsc1 pAbs. This suggested that sera of SPD-type IgA pemphigus might contain autoantibodies against Dsc1.

We have shown, with immunofluorescence of non-fixed COS7 cells expressing human Dsc1, 2, or 3, that all the sera of SPD-type IgA pemphigus reacted with Dsc1, but none of the sera of IEN type showed this reactivity. IgA antibodies in both types of IgA pemphigus reacted with neither Dsc2 nor Dsc3. The most likely reason, therefore, for the failure to detect human Dsc with immunoblotting of human epidermal extracts is that these epitopes on Dsc molecules may be altered by extraction, isolation, and immunoblotting procedures.

These results convincingly show that human Dsc1 is an autoantigen for SPD-type IgA pemphigus, which may therefore play an important role in the pathogenesis of this disease. This study also shows that a human Dsc can be a target antigen for an autoimmune blistering skin disease.

We initiated this study because we found that some IgA pemphigus sera react with bovine Dsc molecules in immunoblotting. It is still not clear, however, why some IgA pemphigus sera reacted with bovine, but not human, Dsc under these conditions. It may be that greater amounts of Dsc proteins were obtained in the bovine desmosome preparations than in extracts of human epidermis. Alternatively, it may be that bovine desmosomal glycoproteins retain more of their normal conformation on immunoblots because of some undefined species difference. The autoantibodies would then react with epitopes in the bovine desmosomes while similar epitopes disrupted in blotted human glycoproteins.

We anticipated that sera of IEN-type IgA pemphigus might react with Dsc3, because the staining pattern in human epidermis was similar to that of anti-Dsc3 pAb. This study does not indicate, however, that the target antigen for IEN-type IgA pemphigus is Dsc. Our previous immuno-electron microscopic study also indicated that the antigen for IEN type is not present in desmosomes (Akiyama et al, 1992). Therefore, it is plausible that the antigen for the IEN type is not a desmosomal protein. The results of this study reinforce the view that distinct antigen profiles are responsible for the clinico-pathologic differences between the IEN and SPD types of IgA pemphigus.

Although the target antigen of these IgA autoantibodies has been identified, their pathogenic role has not been directly confirmed. This question should now be resolved using the mouse model, as has been done for pemphigus autoantibodies. This study also shows that immunofluorescence using cells transfected with cDNA encoding possible antigen proteins is a useful method for defining antigens whose epitopes are conformation-dependent and so cannot be detected with conventional immunoblotting.

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