Corneodesmosin, a Component of Epidermal Corneocyte Desmosomes, Displays Homophilic Adhesive Properties*

Received for publication, August 31, 2001, and in revised form, December 4, 2001
Published, JBC Papers in Press, December 5, 2001, DOI 10.1074/jbc.M108438200

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Corneodesmosomes, the modified desmosomes of the uppermost layers of the epidermis, play an important role in corneocyte cohesion. Corneodesmosin is a secreted glycoprotein located in the corneodesmosomal core and covalently linked to the cornified envelope of corneocytes. Its glycine- and serine-rich NH₂-terminal domain may fold to give structural motifs similar to the glycine loops described in epidermal cytokeratins and loricrin and proposed to display adhesive properties. A chimeric protein comprising human corneodesmosin linked to the transmembrane and cytoplasmic domains of mouse E-cadherin was expressed in mouse fibroblasts to test the ability of corneodesmosin to promote cell-cell adhesion. Classic aggregation assays indicated that corneodesmosin mediates homophilic cell aggregation. Moreover, Ca²⁺ depletion showed a moderate effect on aggregation. To assess the involvement of the glycine loop domain in adhesion, full-length corneodesmosin, corneodesmosin lacking this domain, or this domain alone were expressed as glutathione S-transferase fusion proteins and tested for protein-protein interactions by overlay binding assays. The results confirmed that corneodesmosin presents homophilic interactions and indicated that its NH₂-terminal glycine loop domain is sufficient but not strictly necessary to promote binding. Altogether, these results provide the first experimental evidence for the adhesive properties of corneodesmosin and for the involvement of its glycine loop domain in adhesion.

In the course of their differentiation program, epidermal keratinocytes undergo cornification, a complex set of biochemical events associated with major morphological modifications, resulting in their transformation into corneocytes. Corneocytes, devoid of tripartite plasma membrane, are limited by a highly cross-linked insoluble protein shell, the cornified envelope (1–3). Cornification induces structural modifications of the keratinocyte desmosomes, including the disappearance of the cytoplasmic plaque that is incorporated in the cornified envelope, and the densification of the desmoglea. However, the mechanisms underlying their transformation into corneodesmosomes are still poorly understood. Corneodesmosomes mediate the strong intercellular cohesion in the cornified layers that is crucial for the physical and chemical barrier function of the epidermis. Ultimately, they are degraded at the time of desquamation (4).

Human corneodesmosin (Cdsn),¹ a 52- to 56-kDa basic glycoprotein specific to the cornified epithelia and the inner root sheath of the hair follicles, is firstly detected in the secretory vesicles (i.e. keratinosomes) of the keratinocytes of the uppermost spinous layer and granular layer. It is also present in the extracellular part of the granular keratinocyte desmosomes and remains in these structures after their transformation into corneodesmosomes. In the cornified layers, Cdsn is covalently linked to the cornified envelope (5–7).

Cdsn has a very high serine and glycine content (27.5 and 16%, respectively). This feature is shared with several epidermal proteins: filaggrin, the intermediate filament-associated protein that participates in the formation of the corneocyte fibrous matrix; loricrin, a major component of the cornified envelope; and both termini of epidermal cytokeratins. The serine- and glycine-rich domains of cytokeratins and loricrin have been proposed, as a consequence of the association of interspersed aromatic or aliphatic residues, to form structural motifs, the so-called “glycine loops,” that would mediate intermolecular adhesion by acting like a Velcro (8). Two mutations in cytokeratin genes affecting glycine loop coding sequences were recently shown to be associated with human skin diseases (9, 10). These data reinforce the hypothesis that cytokeratin glycine loops are required for normal intermediate filament organization and function. In Cdsn, serine and glycine residues are distributed all along the sequence but represent more than half of the amino acids within three regions. One of them, from amino acid 60 to 171, perfectly matches features of Steinert’s glycine loop model, and could confer adhesive properties to Cdsn. This hypothesis is supported by the subcellular location of the protein.

Here, we report that human Cdsn actually is an adhesive molecule. Indeed, when expressed at the surface of mouse fibroblasts, Cdsn mediates homophilic cell aggregation. Using full-length and truncated forms of recombinant Cdsn in protein-protein interaction experiments, we confirm that Cdsn

¹ The abbreviations used are: Cdsn, corneodesmosin; E-cad, E-cadherin; GST, glutathione S-transferase; mAb, monoclonal antibody; PBS, phosphate-buffered saline; HBSS, Hanks’ balance salt solution.

* This study was supported in part by grants from the Université Paul Sabatier-Toulouse III (JE 1965 DGRT), from the Société de Recherche Dermatologique, from the Region Midi-Pyrénées, and from INSERM (CJF 9602). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

‡ Supported by a post-doctoral fellowship from the Société de Secours des Amis des Sciences and from the Fondation Singer Polignac.

§ A recipient of a scholarship from the French Ministry of Research and Technology.

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self-associates and we demonstrate for the first time that a glycine loop domain displays adhesive properties in vitro.

**EXPERIMENTAL PROCEDURES**

**Construction of Expression Vectors and Protein Purification**—The eucaryotic pBATEM2 expression vector for full-length mouse E-cadherin (E-cad) (11) and the empty pBATNeo vector were gifts from Dr. M. Takeichi (Kyoto, Japan). The p14.9 plasmid, a derivative of pcDNA.1 containing the complete coding sequence of human Cdsn was as described (12). To construct an expression vector for a Cdsn/E-cad fusion protein, the portion of e-cad sequence encoding the transmembrane and cytoplasmic domains (nucleotides 2172–2721, GenBank™ accession number X06115.1) was amplified by PCR from pBATEM2 using the following primers 5′-GCTCTAGACCTGTCCTGCCACCC-3′ and 5′-CCGGAATTCCTGAGCGGCACGGTTGCAC-3′. After digestion with EcoRV and XbaI, the PCR product was cloned between the corresponding sites of pGEX-2T to give pGEX-Cdsn generated from p14.9 using the primers S117UBam and a chimeric strategy was used as previously described (13). A PCR product was amplified from p14.9 using the primer S195USma 5′-CCGGATCCATTGGCACCTTCTCAGACC-3′ and S527LEco 5′-GAAGCTGCTGC-3′. After digestion with EcoRI, the PCR fragment comprising Cdsn nucleotides 195–601 of human Cdsn fused to amino acids 702–905 of mouse E-cad (Fig. 1a).

The portion of the Cdsn cDNA corresponding to nucleotides 117–1609 (GenBank™ accession number AF030130) was amplified with the primers S117UBam (5′-CCGGATCCATTGGCACCTTCTCAGACC-3′) and S6109LEco (5′-CCGGAATTCCTGAGCGGCACGGTTGCAC-3′) and S6109LEco (5′-CCGGAATTCCTGAGCGGCACGGTTGCAC-3′) and S6109LEco (5′-CCGGAATTCCTGAGCGGCACGGTTGCAC-3′). After digestion with BamHI and EcoRI, the PCR product was cloned between the corresponding sites of pGEX-2T (Amersham Biosciences, Inc.) to give the plasmid pGEX-Cdsn encoding a fusion protein comprising amino acids 1–501 of human Cdsn fused to amino acids 929–171 (GST fusion protein with the NH2-terminal glycine loop domain of Cdsn, a fusion containing the complete coding sequence of human Cdsn was as described above, washed three times in HBSS containing 1% bovine serum albumin, and resuspended at 5 × 10^6 per ml in the same buffer supplemented with 1 μg/ml of the expression plasmids, and 6 μl of FuGENE (Roche Molecular Biochemicals) were diluted to 1:200.

To construct the plasmid pGEX-Cdsn fusion protein with the NH2-terminal glycine loop domain of Cdsn, a fusion containing the complete coding sequence of human Cdsn was as described above, washed three times in HBSS containing 1% bovine serum albumin, and resuspended at 5 × 10^6 per ml in the same buffer supplemented with 1 μg/ml of the expression plasmids, and 6 μl of FuGENE (Roche Molecular Biochemicals) were diluted to 1:200.

**RESULTS AND DISCUSSION**

**Generation of L cells Expressing Cdsn at Their Surface**—To study the potential role of Cdsn in homophilic cell-cell interactions in L cells, we expressed a chimeric protein comprising the human Cdsn and the transmembrane and cytoplasmic domains of mouse E-cadherin (E-cad) (Fig. 1a). The rationale of this approach was first that Cdsn is tightly linked to corneodesmosomes and, second, that Cdsn expressed by transfected HeLa cells is secreted in the culture medium and is not localized on desmosomes (12). In the present experiments, L cells were chosen, because they do not express any cadherins and do not present junctional structures such as desmosomes. Moreover, they were previously used to demonstrate the adhesive properties of cadherins after transfection with the corresponding cDNAs (reviewed in Ref. 15), showing that they express the intracellular proteins necessary for cadherin to mediate cell adhesion. To check for the expression and localization of Cdsn/E-cad fusion protein, indirect immunofluorescence was performed with the anti-Cdsn antibody: G36-19 mAb at 0.2 μg/ml that recognizes amino acids 306–309 (12) or an affinity-purified polyclonal antibody directed against Cdsn amino acids 40–55 (antisera A 40, 55) at 4.2 μg/ml, produced and characterized as described previously (14).

**Trypsin Treatment**—Cells were released from the substrate with 1 mL of Hanks’ balanced salt solution (HBSS, Invitrogen), centrifuged for 5 min at 1000 rpm and re-suspended in HBSS containing either 1 μM EDTA, or 0.05% trypsin and 1 μg/ml CaCl2, or 0.05% trypsin and 1 mM EDTA. After a 15-min incubation at 37°C, soybean trypsin inhibitor (1X) (Sigma) (24) was added, and the cells were analyzed for E-cad or Cdsn/E-cad expression by immunoblot.

**Cell Aggregation Assays**—Cells were released from the substrate as described above, washedthree times in HBSS containing 1% bovine serum albumin, and resuspended at 5 × 10^6 per ml in the same buffer supplemented with 1 μg/ml of the expression plasmids, and 6 μl of FuGENE (Roche Molecular Biochemicals) were diluted to 1:200.

**Overlay Binding Assays**—Proteins were separated by SDS-PAGE and transferred onto nitrocellulose membranes. After 30 min of blocking in TBSTL (40 mM Tris-Cl, pH 8.0, 150 mM NaCl, 0.05% Tween 20, 5% dry milk powder). Cells were incubated for 1 h at room temperature with the recombinant proteins dissolved in TBSTL. Proteins adsorbed on the membranes were specifically revealed with an appropriate anti-Cdsn antibody: G36-19 mAb at 0.2 μg/ml that recognizes amino acids 306–309 (12) or an affinity-purified polyclonal antibody directed against Cdsn amino acids 40–55 (antisera A 40, 55) at 4.2 μg/ml, produced and characterized as described previously (14).
protein was analyzed by immunoblot using C20820 mAb. As expected, the protein remained intact after incubation with EDTA alone. Interestingly, the full-length Cdsn/E-cad was degraded by trypsin both in the presence and the absence of Ca\(^{2+}\) (Fig. 1d, left panel). In agreement with the prediction of 12 Cdsn tryptic fragments, the anti-Cdsn G36-19 mAb gave no signal after trypsin digestion (data not shown). When control experiments were performed with a stable clone of L cells (LEC3) expressing E-cad, the full-length protein was proteolyzed only in the presence of trypsin and EDTA (Fig. 1d, right panel), in full agreement with previous data showing that classic cadherins are resistant to trypsin degradation in the presence of Ca\(^{2+}\) (15).

Taken together, these immunohistochemical and immunoblot experiments established that Cdsn/E-cad was correctly expressed at the cell surface with the expected orientation. Moreover, its full sensitivity to trypsin in non-permeabilized cells showed that none was retained in intracellular membrane compartments.

**Cdsn/E-cad Mediates Aggregation of L Cells by Homophilic Interactions**—To assess the ability of Cdsn/E-cad to mediate intercellular adhesion, we used a standard cell aggregation assay. After a 2-h incubation in the presence of 1 mM CaCl\(_2\), clones pCH1-45 and pCH1-47 formed aggregates (Fig. 2, a and b), whereas the non-transfected cells remained segregated (Fig. 2c). Under the same conditions, the cells expressing the full-length E-cad also formed aggregates, which were, however, distinctly larger than those observed with the fusion protein (Fig. 2d). Moreover, from quantification of the aggregates, it was clear that Cdsn/E-cad fusion protein was less effective to promote aggregation than the full-length E-cad (Fig. 4, compare pCH1-45 full line and LEC3 full line). Although these data showed that Cdsn/E-cad can mediate cell adhesion, they did not establish that homophilic interactions between the Cdsn extracellular moieties were involved. It was indeed conceivable that cell adhesion is mediated by a heterophilic interaction between Cdsn and a cell-surface protein of the L cells. To distinguish between these possibilities, we performed experiments of co-aggregation between cells expressing Cdsn/E-cad and the parental L cells. In a first series of experiments, transfected cells were labeled with the PKH26 red fluorescent dye and allowed to aggregate in the presence of an identical number of unlabelled parental L cells (Fig. 3, a and b). Under these conditions, the main body of the aggregates was composed of labeled cells only, although occasional unlabeled cells could be observed at the periphery (arrows in Fig. 3a). Control experiments performed only with transfected cells showed that all the cells were labeled and that the labeling did not affect their aggregation (Fig. 3, c and d). In converse experiments, labeled parental cells were mixed with unlabeled transfected cells (Fig. 3, e and f). Under these conditions, the aggregates were devoid of labeled cells (arrows in Fig. 3e), although mixed clusters of small size were occasionally observed (arrowhead in Fig. 3e). A control experiment performed with labeled parental cells alone (Fig. 3, g and h) showed that the labeling did not promote cell aggregation. Taken together, these experiments show that L cells expressing Cdsn/E-cad selectively aggregate with each other, but not with the parental L cells. They strongly suggest that aggregation is mediated by homophilic interactions of the Cdsn extracellular domain of the fusion protein, rather than by heterophilic interactions of the Cdsn moiety with a normal endogenous membrane component of L cells. However, we cannot exclude the unlikely possibility that expression of the chimeric protein induces the expression of a cell surface protein, which actually displays the adhesion.

**Ca\(^{2+}\) Depletion Does Not Strongly Influence Aggregation Mediated by Cdsn**—Cellular adhesion mediated by classic cad-
Herins strictly Ca\(^{2+}\)-dependent (15). It was therefore interesting to investigate whether this also holds true for Cdsn/E-cad. In a quantitative aggregation test performed with L cells expressing the fusion protein, only a faint but reproducible decrease in adhesive properties was observed when the cells were incubated without Ca\(^{2+}\) but in the presence of 1 mM EDTA. As an example, a 20% decrease in aggregation was noticed after a 4-h incubation in the absence of Ca\(^{2+}\) (Fig. 4). This weak effect is most probably due, at least in part, to a deleterious effect of EDTA. In the same conditions, the aggregation of L cells expressing full-length E-cad was, as expected, strongly inhibited by Ca\(^{2+}\) depletion (a 70% decrease), whereas parental L cells did not aggregate in the presence or in the absence of Ca\(^{2+}\). Therefore, Cdsn-mediated cell aggregation is largely Ca\(^{2+}\)-independent, in strong contrast with that mediated by E-cad.

**Glycine Loop Domain Involvement in Cdsn Adhesion**—To reinforce the results obtained with the fibroblastic model, we investigated biochemically the homophilic interactions of Cdsn. To do so, overlay binding assays were performed with purified GST-Cdsn recombinant proteins (Fig. 5a). The GST-CdsnΔ93 protein, lacking the NH\(_2\)-terminal epitope recognized by the antiserum A\(_{40–50}\), was resolved by SDS-PAGE and transferred to a nitrocellulose membrane. The membrane was then incubated with the GST-CdsnΔ33 protein, corresponding to the full-length form devoid of the signal peptide, as a probe. Binding of the probe onto its target adsorbed on the membrane was specifically revealed with the antiserum A\(_{171–258}\). A dose-dependent interaction between GST-CdsnΔ93 and GST-CdsnΔ33 was clearly observed (Fig. 5b). When the binding assay was repeated using GST rather than GST-CdsnΔ93 as the target, no signal was observed, showing that the interaction between GST-CdsnΔ93 and GST-CdsnΔ33 was not mediated by GST interactions (Fig. 5b). In additional experiments, no interactions were detected between the GST-CdsnΔ33 probe and a recombinant GST-human filaggrin produced as previously described (16) or bovine serum albumin (data not shown). The former control was particularly relevant, because filaggrin, like Cdsn, is a serine- and glycine-rich protein but is devoid of glycine loop domains.

The NH\(_2\)-terminal serine- and glycine-rich domain of Cdsn (amino acids 60–171) presents a series of serine and glycine repeats that could fold into glycine loops likely to mediate intermolecular interactions as proposed for cytokeratin and loricrin (8). We therefore wondered whether this domain of Cdsn was necessary and sufficient for homophilic interactions in the protein overlay binding assay. Only a low signal was detected after incubation of the GST-CdsnΔ93 target with increasing concentrations of GST-Cdsn protein lacking the NH\(_2\)-terminal glycine loop domain (Fig. 5c). This result establishes that deletion of this domain dramatically reduces Cdsn homophilic interaction in the overlay binding assay. To determine if this domain was sufficient, recombinant GST-Cdsn60–171, containing only the NH\(_2\)-terminal glycine loop domain of Cdsn (Fig. 5a), was used as the target in the protein binding assay. Binding was revealed in the test using the anti-Cdsn G36-19 mAb. Strong signals were obtained with the GST-CdsnΔ33 and GST-CdsnΔ93 probes (Fig. 5d). Deletion of the NH\(_2\)-terminal domain in the probe strongly reduced the interaction with the GST-Cdsn60–171 target, but a significant interaction was still detected.

Taken together, these data confirm the homophilic interaction properties of Cdsn previously suggested by the cellular aggregation test. They further show that, in vitro, the NH\(_2\)-terminal glycine loop domain is sufficient to interact with the full-length mature form of Cdsn. However, this domain is not strictly necessary, because its deletion strongly reduced but did not abolish the interaction. Cdsn homophilic interaction is probably mediated by a direct interaction between the NH\(_2\)-terminal domains of two Cdsn molecules, and by a minor, but significant interaction between the NH\(_2\)-terminal domain and another region of the protein. Serine and glycine represent more than 50% of the residues in two other parts of the molecule, from amino acids 193 to 249 and 375 to 465. These large domains may contribute to the homophilic interaction, even if they do not perfectly fulfill the criteria defined by Steinert et al. (8), i.e. that at least two consecutive loops must be formed by the association of aromatic residues.

Glycine loops are also present in other epidermal proteins (i.e. cytokeratins and loricrin) and thus may have a general function in intermolecular interactions. The functional model based on the Velcro hypothesis was proposed by Steinert et al. (8) in two epidermal scenarios: (i) interactions between the glycine loops of adjacent cytokeratin molecules may form the basis for adaptable intra-cytoskeletal interactions and participate in cytokeratin intermediate filament assembly, and (ii) the glycine loops of cytokeratins could interact with similar
structures in loricrin, linking cornified envelope to the intracellular fibrous matrix. Although direct evidence for the involvement of glycine loops in protein-protein interactions is still lacking in vivo, two mutations located in glycine loop coding sequence of cytokeratin genes were recently reported to be associated with human skin diseases. The first one results in a 4-amino acid deletion in the NH2-terminal domain of cytokeratin K16, including an aromatic residue potentially involved in the formation of a glycine loop. This mutation was responsible for a particular form of palmoplantar keratoderma, a disease characterized by marked hyperkeratosis (9). The second mutation described in the cytokeratin K1 gene (KRT1) is responsible for a severe form of epidermal hyperkeratosis known as ichthyosis hystrix Curth-Macklin. This mutation leads to the expression of a cytokeratin K1 form with a mutated tail variable domain. This V2 domain presents, instead of the unique glycine-rich motifs and flexible structure characteristic for wild type K1, a highly hydrophobic region probably folded in a globular structure. Expression of the mutated cytokeratin K1 results in a profound abnormality of the cytoskeletal architecture (10). Our present experimental evidence for glycine loop homophilic binding in vitro supports the relevance of Steinert’s model and provides functional data for the involvement of glycine loops in intermolecular adhesion.

Cdsn has been shown by immunoelectron microscopy to be linked to the corneodesmosomal zone of cornified envelopes previously extracted using high concentrations of urea, SDS and dithiothreitol, and boiling (6). Moreover, after trypsin digestion, these envelopes were shown to contain Cdsn-derived peptides corresponding to the central domain of the molecule (7, 14). These data show that Cdsn is covalently linked to corneodesmosomes and cornified cell envelopes. We presently show that Cdsn exhibits homophilic adhesive properties. Taken together, our previous and present results strongly suggest that Cdsn acts as a cell-cell adhesion molecule in vivo.

Cdsn undergoes a sequential proteolytic cleavage during maturation of corneocytes, and this event seems to be a major prerequisite for desquamation (17). In the cornified layers, both Cdsn NH2 and COOH extremities are sequentially degraded. Finally, only the central part of Cdsn, approximately from amino acids 300 to 425, probably devoid of adhesive properties, is present at the surface of detached corneocytes (14). This recent finding further supports the hypothesis that the adhesive properties of Cdsn are essential for corneodesmosome function and emphasizes the physiological importance of the NH2-terminal glycine loop domain in Cdsn function. Besides Cdsn, the only components of the corneodesmosome core identified to date are the extracellular domains of the desmosomal cadherins (i.e. desmoglein 1 and desmocollin 1). Together with Cdsn, they may be crucial for mediating the strong intercellular cohesion of corneocytes. Unlike the desmosomal cadherins, Cdsn has the unique feature of being secreted. The extracellular domain of desmosomal cadherins is obvious candidates for Cdsn attachment to the desmosomes, but this remains to be established.

Its distribution in the epidermis, as well as its genomic location at the human major histocompatibility complex locus (6p21), make Cdsn a good candidate in susceptibility to familial psoriasis, an inflammatory skin disease with impaired desquamation and hyperkeratosis. Genetic associations between polymorphic positions of the CDSN gene and susceptibility to psoriasis were recently reported (18–20). Our present results, showing that Cdsn displays homophilic interactions and suggesting that Cdsn is particularly important in the cohesion of the cornified layers, support this hypothesis and emphasize the interest for a better understanding of Cdsn function both in normal skin and diseased skin.

Acknowledgments—We greatly acknowledge Dr. M. Takeichi and Dr. B. Mehul for the generous gift of plasmids.

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