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Desmocollins form a distinct subset of the cadherin family of cell adhesion molecules

(desmosomes/adherens junctions/cell–cell interactions)

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ABSTRACT **The desmosomal adhesive core is formed by four major components: desmoglein (M_r, 165,000), desmocollins I and II (M_r, 120,000 and 110,000, respectively), and a M_r 22,000 protein. Here, we report the cloning and sequencing of cDNAs encoding a bovine desmocollin. The open reading frame found in the longest cDNA, 5 kilobases, contains a region encoding a protein of 839 amino acids. The features of the deduced amino acid sequence imply that the mature 707-amino acid desmocollin is a type I transmembrane protein that is produced by proteolytic cleavage of an 810-amino acid precursor. The ectodomain of desmocollin contains repeats that show extensive sequence similarity to members of the cadherin family of calcium-dependent cell adhesion molecules. A comparison of the amino acid sequences of desmocollin, desmoglein, and the cadherins shows that although these intercellular junctional adhesion molecules share a consensus sequence in their adhesive domains that defines them as a family, several features, including the divergence in the sequence of their cytoplasmic tails, divide them into three distinct subtypes.**

Desmosomes are attachment devices between cells that are characterized by a widened intercellular space bisected by a midline density and a pair of electron-dense submembranous mats called plaques, which are the foci of anchorage of intermediate filaments to the membrane (1). The subcellular fraction enriched in the intercellular adhesive cores consists of four major glycoproteins, desmoglein (M_r, 165,000), desmocollins I and II (M_r, 120,000 and 110,000, respectively), and a M_r 22,000 component (2).

Desmocollins I and II are a pair of closely related proteins. Both polypeptides have similar isoelectric points and overall amino acid composition, and proteolysis of each produces similar patterns of fragments (3, 4). Their size difference has been attributed to differential glycosylation and phosphorylation (3, 5). To date, all polyclonal and monoclonal antibodies raised against the desmocollins recognize both desmocollins I and II (5–9). Fab' fractions of an anti-desmocollin antiserum detect desmocollins on the cell surface prior to cell contact and inhibit desmosome assembly when added to the culture medium of subconfluent cells (10). This led to the suggestion that desmocollins play a key role in initiating desmosome assembly and possibly in desmosomal adhesion (10).

Desmosomal assembly and stability are extremely sensitive to calcium ion concentration (11, 12), and desmocollins and desmoglein bind calcium ions in gel-overlay assays (13). There are three families of cell adhesion molecules that show a similar requirement for calcium ions to manifest their adhesive properties: the integrins, the lectins, and the cadherins (14, 15). We (16) and others (17) have shown that desmoglein shares amino acid sequence similarity with the cadherins, which are the major adhesive components of the adherens junction.

Herein we present the complete amino acid sequence of a desmocollin precursor deduced from the nucleotide sequence of cDNA clones‡ and demonstrate that desmocollin represents a unique subset within the cadherin family of adhesion molecules. Thus, the adherens junction and the desmosome, which are morphologically similar, contain adhesive components that are structurally related.

MATERIALS AND METHODS

Desmocollin-Enriched Fractions. Individual desmocollin protein bands were gel-purified (6) from subcellular fractions enriched in bovine snout desmosomal glycoprotein cores (18).

Antibody Production. Anti-desmocollin antibodies were produced as described (6). The resulting antibodies were characterized by immunoblot analysis of bovine epidermal desmosomal fractions and by immunofluorescence microscopy and gave similar results with these techniques to those described (6).

Peptide Isolation and Sequencing. Desmocollin proteins were digested with trypsin. Resulting peptides were purified by reverse-phase HPLC and sequenced by William Lane (Harvard Microchemistry Facility, Cambridge, MA). The sequence of the amino-terminal 12 amino acids of the mature protein and those of three tryptic peptides are underlined in Fig. 1 and denoted by the numerals *i*, *ii*, *iii*, and *iv*.

cDNA Library Construction and Isolation of cDNA Clones Encoding Bovine Epidermal Desmocollin. The complete desmocollin cDNA was obtained by a 3-fold screening strategy. First, a bovine epidermal cDNA library was constructed in λgt11 as described (19), from mRNA isolated from the epidermis of 10 cow snouts, and screened with specific anti-desmocollin antibodies. Four clones were identified. The longest, 720 base pairs (bp) termed DC-700, contained an open reading frame coding for 50 amino acids (aa) followed by a stop codon, 554 bp of noncoding sequence, and a poly(A) tail of 16 bases. Overlapping and complementary oligonucleotides were constructed from the 5′ sequence of DC-700 (Fig. 1, bases 2581–2626 and 2644–2595) and used to rescreen the library for longer clones. Seventy positive clones were found in this secondary screen. To produce a probe that could select the longest clones from among these 70 clones, a polymerase chain reaction (PCR) was performed with first-strand bovine epidermal cDNA as the template. The oligonucleotide constructed from bases 2643 to 2595 was used as the 3′ primer and a set of degenerate oligonucleotides encoding the first 6 aa of tryptic peptide *ii* (see above), as the 5′ primer. Ethidium bromide staining of the electrophoresed PCR products detected a single band of 1.3 kilobases (kb) (DC-PCR). Sequence adjacent to the 5′ region of the PCR product was used

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Abbreviation: aa, amino acid.

‡The sequence reported in this paper has been deposited in the GenBank data base (accession no. M61750).

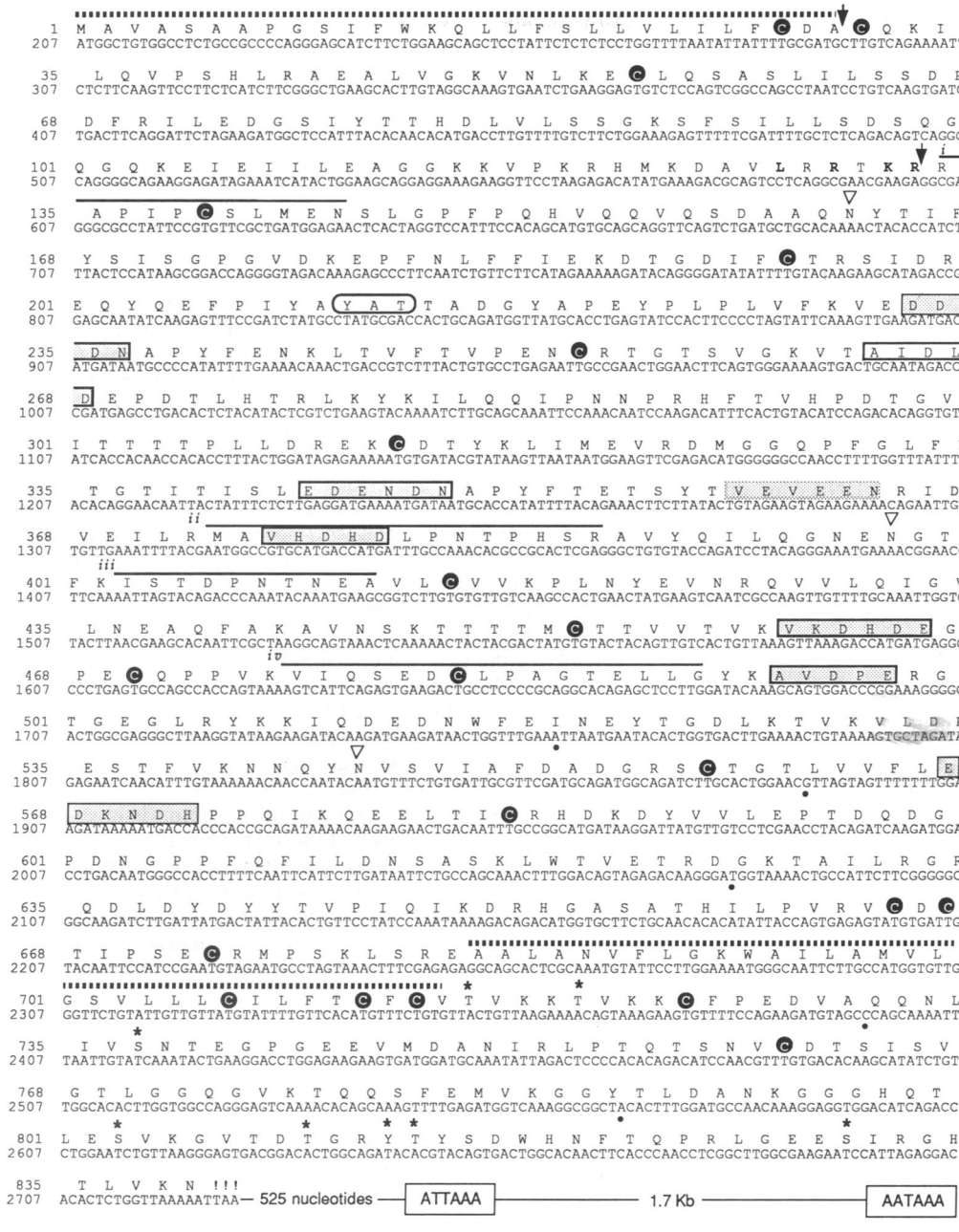

FIG. 1. Nucleotide and protein sequence of desmocollin. The nucleotide sequence for desmocollin is shown with the corresponding 839 aa in the single-letter code. The dashed lines above residues 1–29 and 683–715 show the signal sequence and transmembrane regions, respectively. Sites of probable cleavage of the signal sequence and precursor are indicated by arrows. The solid bar denoted by *i* represents the amino-terminal sequence of the mature protein; bars marked *ii, iii*, and *iv* represent the sequence of three tryptic peptides. Highly acidic regions corresponding to the putative calcium binding regions in the cadherins are indicated by boxed shaded areas, and an additional area high in acidic residues is shown in an unboxed shaded area. Potential N-linked glycosylation sites are indicated by open triangles, and asterisks represent possible phosphorylation sites. Dots below nucleotides in the sequence indicate base changes in the product of the PCR. Cysteines are highlighted in solid circles. The stop codon is denoted by exclamation marks. The positions of the two polyadenylylation signals are indicated diagrammatically.

to create an oligonucleotide (bases 1370–1347). A tertiary screen with the latter probe identified a single positive 5.0-kb clone (DC-23).

DC-700, DC-PCR, and DC-23 were subcloned into pGEM (Promega) and an exonuclease III deletion series was created from both ends of each, using the Erase-a-Base kit (Promega) according to the manufacturer's instructions, to facilitate sequencing of both strands. Double-stranded DNA sequencing was performed using Sequenase (Promega) with either SP6 or T7 primers. The University of Wisconsin Genetics Computer Group package of sequence analysis programs (20) was used on a VAX 6000-410 computer (Digital Equipment).

Northern Blot Analysis. Bovine snout poly(A)$^+$ mRNA (5–10 μg) was electrophoresed in denaturing formaldehyde/agarose gels, transferred to nylon membranes, and used for Northern blot hybridization as described (19).

RESULTS

Characterization of a Desmocollin Precursor. Three cDNAs were sequenced: the 720-bp clone (DC-700) recognized by the desmocollin antibody, a 1.3-kb internal PCR product (DC-PCR), and the longest (5.0 kb) cDNA (DC-23). The nucleotide and deduced amino acid sequence of the complete coding region of a bovine epidermal desmocollin precursor derived from DC-23 is shown in Fig. 1. The authenticity of this clone was established by a 100% match between regions of the deduced protein sequence and the sequence obtained from three tryptic peptide fragments of desmocollin (Fig. 1, amino acids overlined and denoted by the numerals *ii, iii*, and *iv*).

cDNA DC-23 has a single long open reading frame that extends to a stop codon at base 2726. The first methionine at base 207 is followed by a stretch of 29 aa that contains the features required of a signal sequence (21). The 12 aa obtained by sequencing the amino terminus of the mature protein are found at residues 133–144. These results are consistent with desmocollin being synthesized as a precursor of 810 aa that is inserted into the membrane by a cleavable signal sequence of 29 aa and subsequently processed to a mature form of 707 aa by removal of 103 aa from the amino terminus. A single hydrophobic region of 33 aa, sufficient to span the lipid bilayer once, is located at residues 683–715 and is followed by a 124-aa carboxyl-terminal domain. A scan of

the Prosite motif data base revealed three potential sites of N-linked glycosylation (NXS/T) in the amino-terminal domain at residues 163, 398, and 545 and a signal for glycosaminoglycan addition (SGXG) at residues 172–176. A total of eight potential phosphorylation sites were found in the carboxyl-terminal domain. Five sites for protein kinase C phosphorylation (S/TXR/K) were found on threonines at residues 716, 720, and 810 and on serines at residues 803 and 830. Two potential sites of casein kinase 2 phosphorylation (S/TXXD/E) were found on the serine at residue 737 and on the threonine at residue 814. A single motif for tyrosine kinase phosphorylation (R/KXXXD/EXXXY) was found at residue 813.

Desmocollins I and II show a molecular weight difference, variously reported, between 8000 and 15,000 (5, 6, 22). Differential glycosylation of the two proteins and phosphorylation only of the larger desmocollin (3, 9) have been postulated to account for the variation in electrophoretic mobilities. We therefore examined our cDNAs for differences that would be consistent with this explanation. The three clones examined were identical with six exceptions none of which could give rise to differential glycosylation or phosphorylation. The 1.3-kb PCR clone (DC-PCR) that extends from base 1322 to 2643 differed from DC-23 at 5 bases (denoted by dots in Fig. 1), two of these resulted in a change in amino acid residue from isoleucine to phenylalanine at residue 519 and from tyrosine to cysteine at residue 788. These changes could result from mistakes introduced during the 30 cycles of PCR. However, the number of substitutions in our sequence is almost 2-fold that reported to result from these PCR conditions (1/400 bases) (23). Therefore, at least some of the differences may represent polymorphism in the population.

The sixth difference found between the sequences of the clones lies in the site of polyadenylylation. Clone DC-700 is derived from an mRNA in which polyadenylylation initiates 20 bp downstream of the rare ATTAAA polyadenylylation signal found 525 bp beyond the stop codon. Clone DC-23 represents a mRNA that continues for an additional 1.7 kb before polyadenylylation begins 12 bp downstream from the more conventional AATAAA signal. Northern blot analysis of epidermal mRNA detects a message of ≈5.5 kb and a faint band is seen (Fig. 2) slightly above the position of plakoglobin mRNA (3.2 kb). These results indicate that DC-23 (5.0 kb) is nearly complete and that the polyadenylylation signal found in DC-700 is used very rarely and/or results in an unstable species of mRNA.

Desmocollins and Cadherins Show Similarity in Their External Domains but Differ in Their Cytoplasmic Tail. Searches of the data bases found significant similarity between the protein sequences of desmocollin and members of the cadherin family (24). The greatest similarity was found to the N-cadherins. Surprisingly, desmocollin showed a stronger resemblance to all the cadherins than it did to desmoglein. The amino-terminal domain of mature desmocollin (residues 133–683) shares between 34 and 38% identity and 55 and 57% similarity with the extracellular domains of members of the cadherin family. This compares to values of 54% identity and 70% similarity between the extracellular domains of E- and P-cadherins (Table 1).

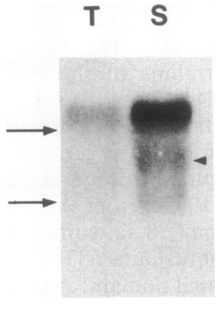

FIG. 2. Northern blot analysis. DC700 cDNA detected a 5.5-kb band in bovine snout epidermal (lane S) or tongue (lane T) mRNA. The arrowhead marks a lower band that probably represents transcripts terminating at the first polyadenylylation signal. The positions of the 28S and 18S rRNA bands are marked by arrows.

Like cadherins, the extracellular domain of desmocollin is highly repetitive. These extracellular repeats have been designated EC1 to EC5; EC5 being closest to the membrane (25). To define the regions of identity in greater detail, we constructed a multiple sequence alignment between the desmocollin extracellular domain and those of all cadherins for which the complete sequence is known (Fig. 3; for a similar comparison of desmoglein to cadherins see ref. 16). The percentage of identical residues was greatest in EC2 followed by EC4 > EC1 > EC3 > EC5. Identical residues were clustered in the putative calcium-binding regions of the cadherins (marked by arrowheads in Fig. 3) that obey the consensus sequences A/VXDXD and DXNDN (26). This feature was also observed in desmoglein (16). It is generally accepted that calcium ions interact with and alter the conformation of cadherins in such a way as to protect them from proteolytic attack (15). Synthetic peptides constructed to these sequences bind calcium, and point mutations within this motif result in loss of the calcium-conferred protection from tryptic digestion (27). The presence of these calcium binding sites within desmosomal glycoproteins is likely to account for the sensitivity of desmosome assembly and stability to the external concentration of calcium ions (12).

Several other highly repetitive cadherin amino acid motifs of unknown function (e.g., LDRE) are present at conserved positions in the desmocollin and desmoglein sequences. The putative proteolytic cleavage signal for cadherin precursor processing, LXRXKR, (Fig. 2) (28) is also present in desmocollin (residues 126–131) and desmoglein. This suggests that the processing of each of these proteins may employ the same protease. Mutations in this cleavage motif inhibit processing and abolish adhesion of cadherins (28). This supports the hypothesis that adhesion molecules are synthesized as precursors to prevent intracellular interaction. Subsequent proteolytic processing would then expose or alter an active site of intermolecular interaction (28).

To determine which residues are crucial to the structure of cadherins, a consensus was constructed of amino acids that are conserved in all members of this family (Fig. 3, line 9). The shaded residues in line 9 indicate that the desmocollin sequence complies with 68% of this consensus, a figure much higher than that derived from comparisons of the overall sequence. Dashes below line 9 indicate amino acids that are conserved in both desmosomal glycoproteins and in all cadherins. Four cysteines found in EC5 (arrows in Fig. 3) and prolines throughout the sequence are highly conserved in cadherins. Both of these features are present in desmocollin but are absent from desmoglein, where they are often replaced by glutamic acid residues (16). Nine cysteines are present in EC1 to EC4 of desmocollins and six cysteines are

Table 1. Comparison of the percentage of identical residues between the extracellular domains of desmocollin, desmoglein, and cadherins

	% identity			
	bDC	mN	mE	mP
mN	39 (57)			
mE	35 (55)	47 (64)		
mP	36 (53)	47 (64)	54 (70)	
bDG	28 (47)	29 (50)	29 (50)	29 (50)

Numbers in parentheses are the percent similarity as defined by the PAM-250 matrix (24). bDC, bovine desmocollin; mN, mouse N-cadherin; mE, mouse E-cadherin; mP, mouse P-cadherin; bDG, bovine desmoglein. The region comprising EC1 to EC5 were aligned using the program GAP with a gap weight of 3.0 and a gap length weight of 0.1.

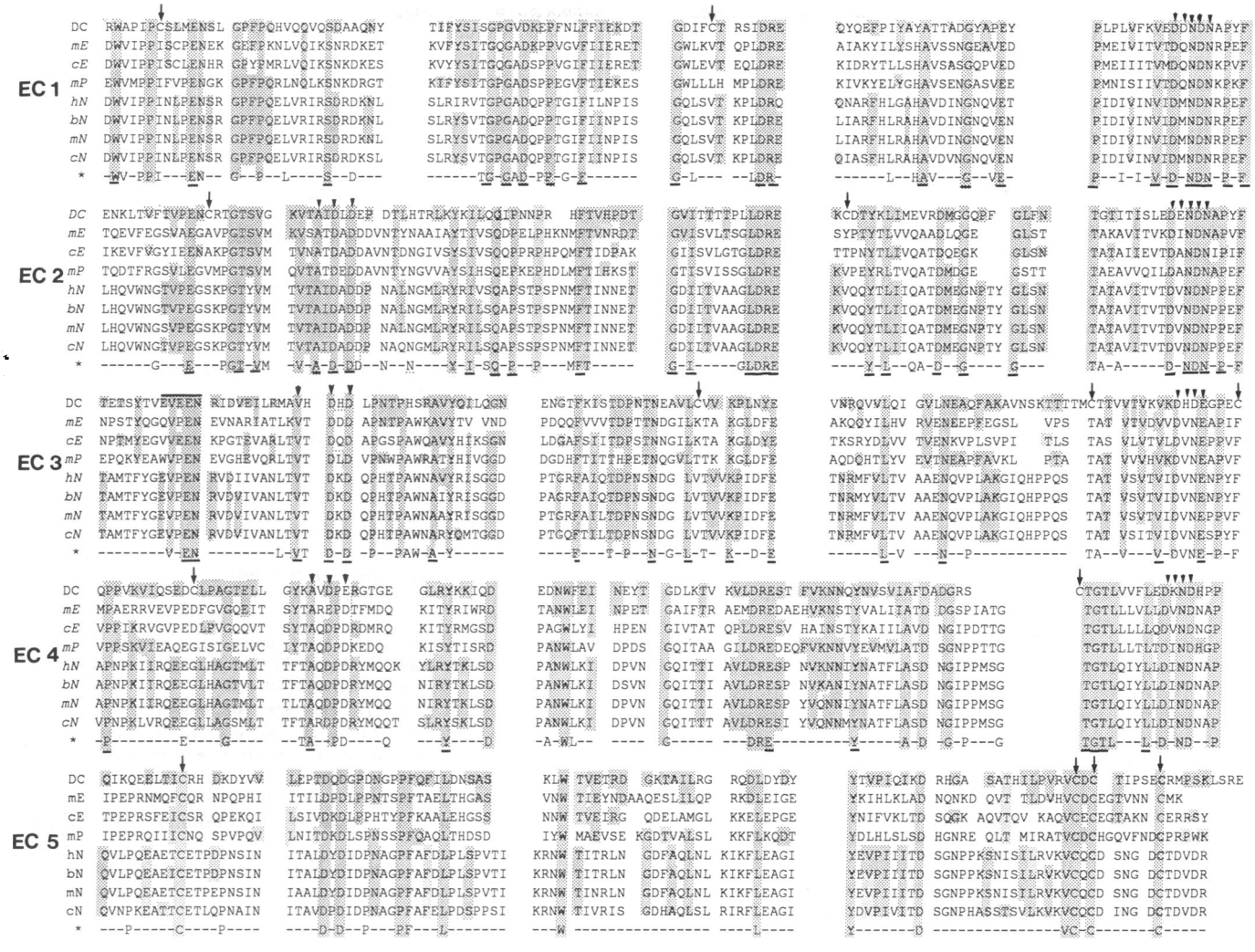

FIG. 3. Multiple protein sequence alignment of bovine desmocollin and cadherins. The five extracellular repeats EC1 to EC5 of desmocollins are shown aligned to the sequences of other cadherins. DC, bovine desmocollin; mE, mouse E-cadherin; cE, chicken E-cadherin; mP, mouse P-cadherin; hN, human N-cadherin; bN, bovine N-cadherin; mN, mouse N-cadherin; cN, chicken N-cadherin. Within each repeat, at most only a few small gaps were required to align any pair of sequences. Nucleotides that are conserved in all cadherins form a consensus shown on the line marked *; dashes under the consensus indicate residues conserved among desmocollin, desmoglein, and the cadherins. Shading indicates residues conserved between desmocollin and other cadherins. The arrows indicate cysteine residues in desmocollin. Arrowheads indicate the putative calcium binding domains of cadherins. Bars indicate additional concentrations of acidic amino acids. Each repeat was aligned with desmocollin and each of the other cadherins using the program GAP with a gap weight of 3.0 and a gap-length weight of 0.1. The resulting pairwise, alignments were imported into the program LINEUP for the final alignment. GenBank accession numbers are as follows: mE, X06115; cE, M16260; mP, X06340; hN, M34064; bN, X53615; mN, M31131; cN, X07277.

found in EC1 to EC4 of desmoglein that are not present in cadherins.

Several other intriguing differences exist among these molecules. In particular, the tripeptide amino acid sequence HAV, which is found in EC1 of cadherins, as well as in hemagglutinins (29) is replaced in desmocollin by the sequence YAT and in desmoglein by the sequence RAL. Single-base mutations of the amino acid residues neighboring the HAV motif have been shown to alter significantly the specific homophilic interactions of cadherins (30).

Finally, the largest sequence divergence is seen in the cytoplasmic tails of these molecules. The desmocollin cytoplasmic domain shows little resemblance to the cadherins or any other protein in the data base. Randomized versions of the desmocollin cytoplasmic tail yielded values of between 11 and 22% identity (average, 18%) and 35 and 48% similarity to the cadherin tails, suggesting that the values obtained with the correct desmocollin sequence (20% identity and 45% similarity after introducing extensive gaps) have little significance and are due to chance. In contrast, desmoglein has stretches of unique sequence, a central region with 28% identity and 53% similarity to the cadherin tail, followed by a unique and repetitive sequence that accounts for the larger size of this molecule (17).

DISCUSSION

Desmocollin has significant similarity in its external domain to a family of cell adhesion molecules termed cadherins. This observation and previous results (10) showing that monovalent anti-desmocollin antibodies inhibit desmosomal assembly strongly suggest that desmocollins are directly involved in the adhesive mechanism of the desmosome.

Our data show that desmocollin, desmoglein, and cadherins are structurally related and may be considered a family. These proteins are all intercellular junctional components, i.e., they are functionally related not only in their adhesive capacity but in their ability to concentrate into specific membrane sites. It is therefore a formal possibility that the

structural resemblance of these proteins is an example of convergent evolution.

Despite the structural similarity of desmosomal glycoproteins and cadherins in their extracellular domains, there are notable differences in key residues that may alter significantly the secondary folding of these proteins. Prolines are highly conserved among the cadherins suggesting they play a crucial role in the folding of these molecules. These residues are largely conserved in desmocollin but have been frequently substituted by acidic glutamic acid residues in desmoglein (16). Furthermore, cysteines, which may alter protein structure through their capacity to form disulfide bridges, are found in large numbers in both desmosomal glycoproteins yet have no counterparts in the cadherin sequences. These differences favor the hypothesis that cadherins, desmocollins, and desmoglein may have arisen from a common ancestral molecule that has diverged into three subtypes in response to junction-specific requirements.

The most striking sequence difference among desmocollin, desmoglein, and the cadherins lies in their cytoplasmic tails. Desmocollins show little resemblance to the cytoplasmic tail of either cadherins or desmoglein. Cadherins show 65% identity to each other in this region, and desmoglein contains unique and cadherin-like regions (17). The cytoplasmic tails of desmocollin, desmoglein, and cadherins are in close proximity to the submembranous plaques associated with intercellular junctions. These plaques contain common and specific components and associate with distinct sets of cytoskeletal filaments. The plaques of adherens junctions contain plakoglobin, vinculin, and catenins (31) and associate with actin filaments. The plaques of desmosomes also contain plakoglobin as well as the desmosome-specific components: desmoplakins I and II, and band 6, and associate with intermediate filaments. Immunoprecipitations of desmoglein by pemphigus foliaceus sera also coprecipitate plakoglobin, suggesting that these two molecules form a complex (32). Similar experiments have detected complexes between cadherins and three polypeptides called catenins (31) and the cytoskeletal proteins fodrin and ankyrin (33, 34). However, the interactions between desmocollins and other components remain to be determined.

Which structural features lead these adhesive proteins to specifically coalesce into the desmosome and the adherens junctions is an intriguing question. Experiments have shown that the cytoplasmic domain of the cadherins is required to enable them to cluster into adherens-type junctions (31). This suggests that cytoskeletal linkage and/or signal transduction is a function of the carboxyl-terminal domain and is required to collect these proteins into junctional sites.

Experimental perturbations of cadherin function not only lead to loss of adhesive properties between cells but also markedly affect cellular differentiation (15). These results suggest that cadherins play an active role in adhesion in the process of cellular recognition and in the transmission of positional information to the cell during embryogenesis. The finding that desmosomal glycoproteins resemble cadherins, therefore, raises questions concerning their role in the process of cellular recognition. It is of some consequence that plakoglobin, a molecule colocalizing with all these molecules is required for the implementation of positional information in *Drosophila* embryos (35). It is possible that the desmosomal adhesive molecules may play a far more dynamic role in the cellular recognition process than was previously imagined.

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