Arch Dermatol Res (2005) 297: 31–38
DOI 10.1007/s00403-005-0573-9

ORIGINAL PAPER

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Desmocollin 1 and desmoglein 1 expression in human epidermis and keratinizing oral mucosa: a comparative immunohistochemical and molecular study

Received: 4 October 2004 / Revised: 9 February 2005 / Accepted: 19 April 2005 / Published online: 31 May 2005

Abstract Epidermis and keratinizing oral mucosa (KOM) are effective barriers against a wide spectrum of insults. The optimal form of protection provided by each epithelium is determined also by the molecular composition of desmosomes. Up to now, the expression of the "skin type" desmosomal cadherins, i.e. desmocollin 1 (Dsc1) and desmoglein 1 (Dsg1), was correlated with the morphological features of keratinocyte terminal differentiation in epidermis, but not in KOM. The aim of the present study was to investigate Dsc1 and Dsg1 expression in adult human KOM compared to epidermis. Biopsies of epidermis and KOM were obtained from young healthy adults ($n=6$) and simultaneously processed for immunofluorescence analysis, post-embedding immunogold electron microscopy (immunogold EM), and RT-PCR analysis. For molecular biology analysis, as a negative control, we considered human fibroblasts. By immunofluorescence and immunogold EM, Dsc1 labeling was not detected in any suprabasal layer of KOM, but it was present in the upper spinous/granular layers of epidermis. Immunofluorescence and transmission electron microscopy analysis showed that (i) Dsg1 expression was evident in the spinous, granular, and horny layer of the oral epithelium and (ii) Dsg1 immunoreactivity was always lower in desmosomes between oral keratinocytes than in all epidermal junctions. RT-PCR analysis confirmed that in KOM Dsc1 gene expression was undetectable. On the whole, these observations suggest a weakened adhesion in KOM, allowing oral keratinocytes to undergo a faster transition throughout the living layers of the epithelium. The intrinsic and specific regulation of the molecular composition of desmosomes can contribute in defining a specific keratinocyte phenotype in KOM and in epidermis.

Keywords human · desmosomal cadherins · keratinocytes · electron microscopy · RT-PCR

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Introduction

Epidermis and keratinizing oral mucosa (KOM) are orthokeratinized stratified squamous epithelia sharing many structural similarities. Both are effective barriers against a wide spectrum of mechanical, physical, and chemical insults [23], but their neighbouring environment is profoundly different. Depending on the specific location, the optimal form of protection provided by each epithelium is determined also by its intrinsic adhesive properties, i.e. by the molecular composition of desmosomes.

Desmosomes, or maculae adherentes, are the most important machinery for intercellular adhesion in stratified squamous epithelia. They are multiprotein, transient junctional complexes composed by plakins, armadillo proteins, and desmosomal cadherins [15]. Desmosomal cadherins are transmembrane glycoproteins, namely desmocollins (Dscs) and desmogleins (Dsgs), occurring as three isoforms (1, 2, 3) encoded by separate genes [4]. Recently, three new desmogleins were identified, namely Dsg1-beta [24], Dsg1-gamma [14] and Dsg4 [31].

In the last decade, considerable progress has been made in studying the molecular composition of desmosomes and the graded distribution of desmosomal cadherins within keratinizing stratified squamous epithelia [22]. Dsc2 and Dsg2 are expressed in all desmosome-possessing tissues [25], whilst Dsc3, Dsg3, Dsc1 and Dsg1 are restricted to stratified epithelia [13, 11]. Both Dsc1 and Dsg1, the "skin type" desmosomal cadherins, have been detected in all nucleated cells of

epidermis [21], in the tongue [17, 27], and in the keratinocyte compartment of human hair follicle [16]. The expression of both Dsc1 and Dsg1 was correlated with keratinocyte terminal differentiation in bovine [17] and human [3] epidermis and in the epithelial compartment of the human hair follicle [16, 33, 7]. Dsg1 was detected in the more superficial layers in KOM by immunoblot and immunofluorescence analysis in mice [18] and in men [27]. Conversely, at present, no experimental and/or clinical observations are available regarding Dsc1 localization in the oral mucous membrane. RT-PCR characterization of the desmosomal components during palatogenesis evidenced the lack of Dsc1 gene expression [20], but the presence of this cadherin still remains to be investigated from a morphological and molecular point of view in adult human KOM.

The present work was aimed at studying the expression of Dsc1 and Dsg1 in KOM compared with epidermis by immunofluorescence, ultrastructural post-embedding immunogold electron microscopy (immunogold EM), and RT-PCR analysis.

Materials and methods

All chemical reagents for immunohistochemical analysis were from Sigma (Sigma Aldrich, St Louis, MO) with the exception of Lowicryl K4M (Agar, Polysciences Inc., Stansted, UK). Copper and nickel grids were from EMS (SIC, Roma, Italy).

Human breast skin ($n = 6$) was obtained after aesthetic surgery of young healthy women (30–40-years-old). Gingival fragments were obtained from the premolar area of the upper dental arch from six healthy and non-smoking volunteers (three males and three females). All individuals showed clinically normal gingiva without any evidence of inflammation or hyperplasia. The age range was 20–27 years. Written informed consent was obtained from all the analyzed individuals. The procedures were preventively approved by the Institutional Review Board.

Immediately after surgery, for each biopsy, a fragment (1 cm^2) was immersion fixed in 4% formalin/0.1 M phosphate buffer saline (PBS) (pH 7.4) for 5 h at room temperature, then routinely dehydrated, paraffin embedded, and serial sections were obtained at 5 μm.

Further fragments were dissected (1 mm^3) by using sterile scalpels and simultaneously processed eitherfor post-embedding immunogold electron microscopy (immunogold EM) on Lowicryl embedded samples or for RT-PCR analysis. In this latter set of experiments, we used a non desmosome-bearing cytotype, i.e. cultured human fibroblasts, as a negative control.

DSC1 and DSG1 immunofluorescence and immunogold EM

Immunofluorescence analysis

To unmask antigenicity, slides were immersed in 200 ml of 0.01 M sodium citrate buffer (pH 6) and irradiated for 10 s in microwave (600 W). After repeated washings in PBS, non-specific binding sites were saturated with a 1:10 goat serum/PBS solution for 30 min at room temperature. Sections were incubated for 45 min at room temperature with mouse prediluted monoclonal anti human desmocollin 1 (Dsc1-U100) or anti human desmoglein 1 (Dsg1-P23). Both antibodies are commercially available (Progen Biotechnik, Heidelberg, Germany). A FITC-conjugated goat anti-mouse antibody (Jackson Immunoresearch Laboratories, PA, USA) was then used at a dilution of 1:200 for 45 min at room temperature. In negative controls, the primary antibodies were omitted and substituted with PBS 0.1 M.

Immunofluorescence analysis was then performed utilizing a Nikon Eclipse E600 equipped with a Nikon digital camera DXM1200 (Nikon, Tokyo, Japan).

Immunogold EM

Samples were fixed by immersion in 2% paraformaldehyde plus 0.1% glutaraldehyde in 0.1 M PBS (pH 7.4) for 2 h, washed with 0.1 M PBS and then immersed in 0.25 M NH_4Cl in PBS overnight at 4°C to remove the

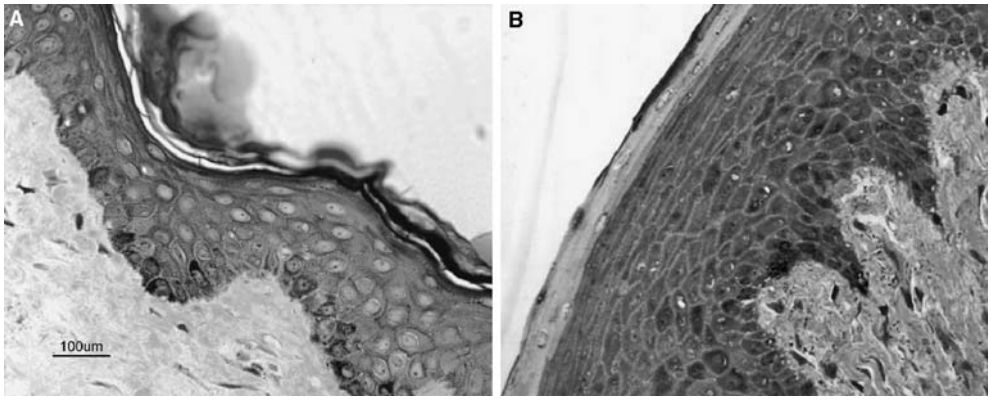

Fig. 1 Photomicrographs of toluidine blue semithin Lowicryl sections. (**a**) Human breast epidermis. (**b**) Keratinized human oral mucosa. Original magnification 20X

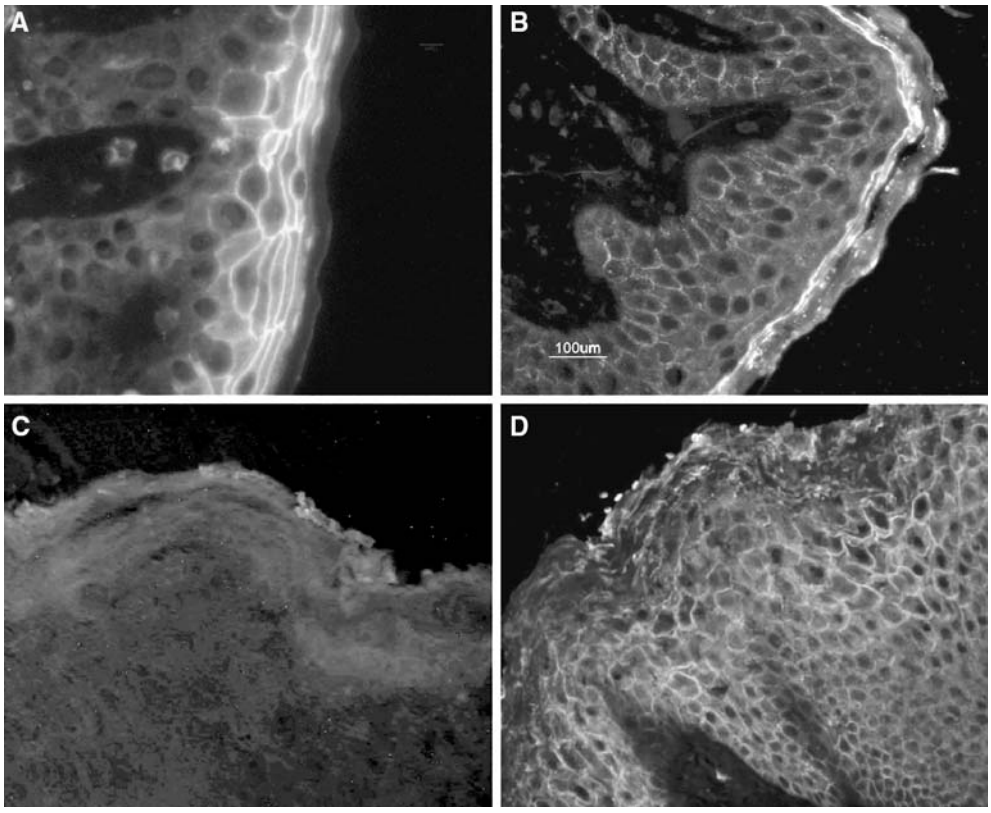

Fig. 2 Immunofluorescence staining for Dsc1 (**a** and **c**) and Dsg1 (**b** and **d**). (**a**) and (**b**) Human breast epidermis. (**c**) and (**d**) Keratinized human oral mucosa. In **c** note the absence of Dsc1 reactivity. Original magnification 60X (**a**), 40X (**b**) and 20X (**c** and **d**)

excess of fixative solution. After washing, they were dehydrated in ascending concentrations of cold ethanol (at −35°C), embedded in Lowicryl K4 M at −35°C and polymerised under UV light (360 nm) at −35°C for a week. Ultrathin sections were cut with a Reichert Ultracut R ultramicrotome and collected on celloidine-coated 100-mesh nickel grids. Lowicryl-processed samples were needed to perform Dsc1 and Dsg1 immunogold EM.

Four immunogold experiments were performed on all Lowicryl samples of each biopsy. Immunogold procedure was performed essentially as previously described [7]. Briefly, sections were incubated at room temperature with 0.03% saponin in 0.05 M TBS/1% BSA (pH 7.6) for 30 min and then for 1 h with the above cited antibodies recognizing either the intracellular part of human desmocollin 1 (Dsc1-100) [22] or the extracellular portion of human desmoglein 1 (Dsg1-P23) [16]. Then, an incubation with a goat anti-mouse IgG, 10 nm gold conjugate, at a dilution 1:20 (Aurion, Wageningen, The Netherlands) was performed for 1 h at room temperature and samples were thoroughly washed. Negative controls were obtained by omitting the primary antibody. Thin sections were examined with a JEM 1010 transmission electron microscope (Jeol, Tokyo, Japan) at 80 kV.

RT-PCR Analysis

Total RNA was extracted from skin and oral mucosa fragments by a modification of the guanidine-isothiocyanate method (Tri-Reagent, Sigma). After DNase I digestion, 1 μg of total RNA was reverse-transcribed in 20 μl final volume reaction mix (Promega, Italy). The primer sequences utilized for RT-PCR are the following: Dsc-1 forward ATG GGC TCC TAT TCC AGC TT, reverse TCT GCA GTT GTT GCA TAG CC; Dsg-1 forward AGA TGC CTG ACT TGC GAG AT, reverse CTA TCA TGC CGG AAG TTG GT; β-actin forward GAG GCC CAG AGC AAG AGA GG, reverse ACC GGA GTC CAT CAC GAT GC. Total RNA extracted from cultured fibroblasts was utilized as negative control.

Amplification reactions were conducted in a final volume of 25 μl containing 2.5 μl of cDNA, 200 μM of the four dNTPs, 100 pmol of each primer, 2.5 U of Taq DNA polymerase (EuroTaq, Euroclone). The RT-PCR products were resolved by electrophoresis in 1% agarose gels, stained with ethidium bromide and quantified in duplicate by densitometric analysis (Image Pro-Plus). β-actin gene expression was utilized to assess sample integrity.

Results

The healthy structure of both epithelia and the structural similarity between epidermis (Fig. 1a) and KOM (Fig. 1b) were confirmed on semithin Lowicryl sections by light microscopy analysis. Orthokeratinization was demonstrated in the two epithelia by the absence of

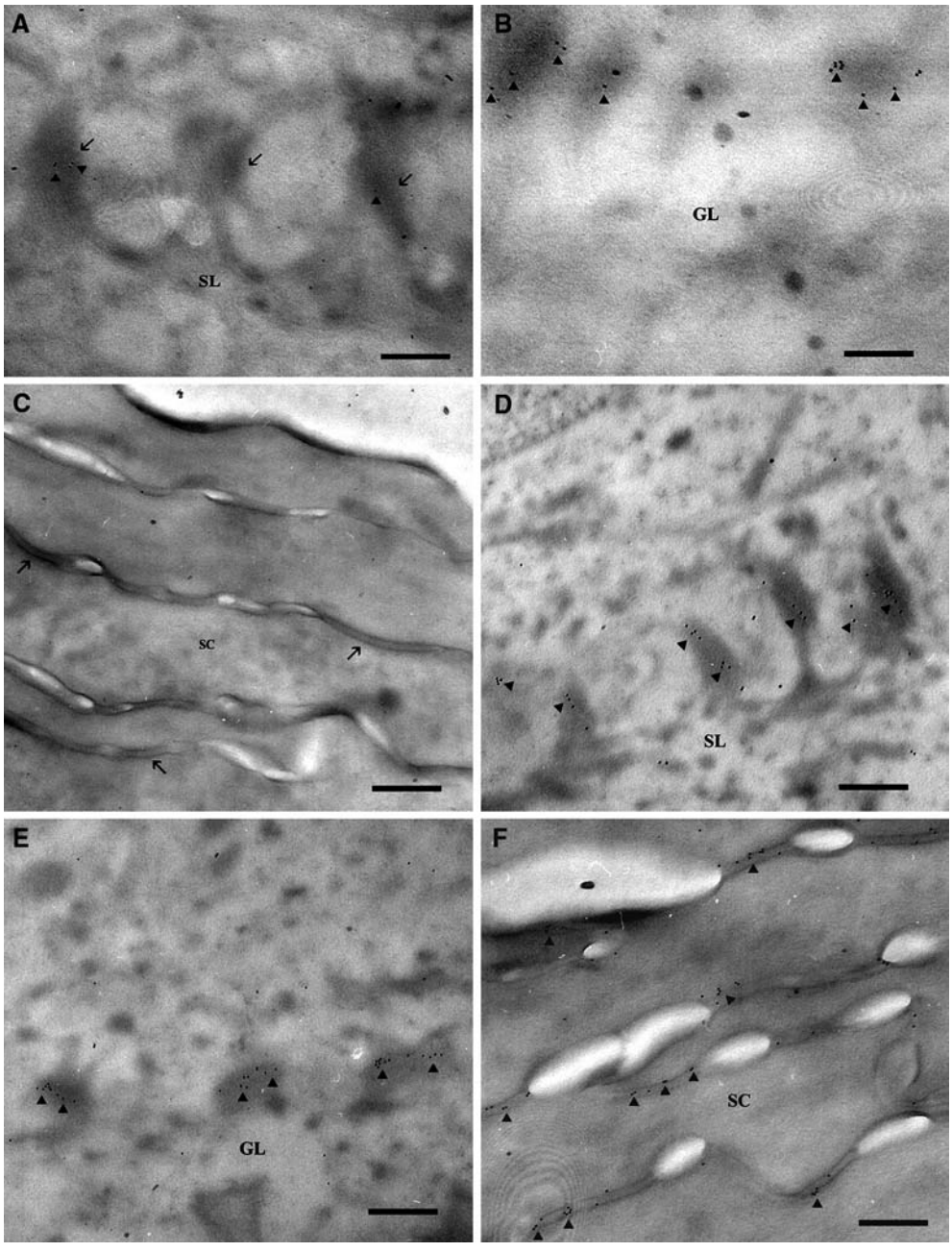

Fig. 3 Electron photomicrographs of Lowicryl ultrathin sections showing Dsc1 (**a**, **b**, and **c**) and Dsg1 (**d**, **e**, and **f**) immunoreactivity in human breast epidermis. Gold particles 10 nm. *Arrowheads* indicate immunolabelling and arrows the presence of desmosomes. (**a**) and (**d**) spinous layer; (**b**) and (**e**) granular layer; (**c**) and (**f**) stratum corneum. In (**c**), note the absence of Dsc1 immunolabelling in corneodesmosomes. Original magnification: 15000X. Bar 285 nm. SL, spinous layer; GL, granular layer; SC, stratum corneum

nuclei in corneocytes on ultrathin Lowicryl sections. No parakeratinized oral mucosa was present.

DSC1 and DSG1 Immunofluorescence immunogold EM

Immunofluorescence analysis

A clear membrane immunoreactivity was always detected in all positive-stained slides. Non specific staining or background was observed after omission of the primary antibody.

Human breast epidermis. Dsc1 immunoreactivity was localized in desmosomes of the more superficial spinous layer and in the granular layer of the epidermis, but not in the stratum corneum (Fig. 2a). All the epithelium resulted Dsg1-positive (Fig. 2b), starting from the immediate suprabasal layers up to the stratum corneum.

Human keratinizing oral mucosa. In KOM, Dsc1 immunoreactivity was not detectable in any keratinocyte layer (Fig. 2c). On the other hand, all suprabasal desmosomes resulted Dsg1-positive (Fig. 2d), with a pattern of distribution similar to epidermis (see Fig. 2b).

Immunogold EM

In all immunogold experiments, the localization of gold particles coincided with the presence of desmosomes. Accordingly with the sequence recognized by the

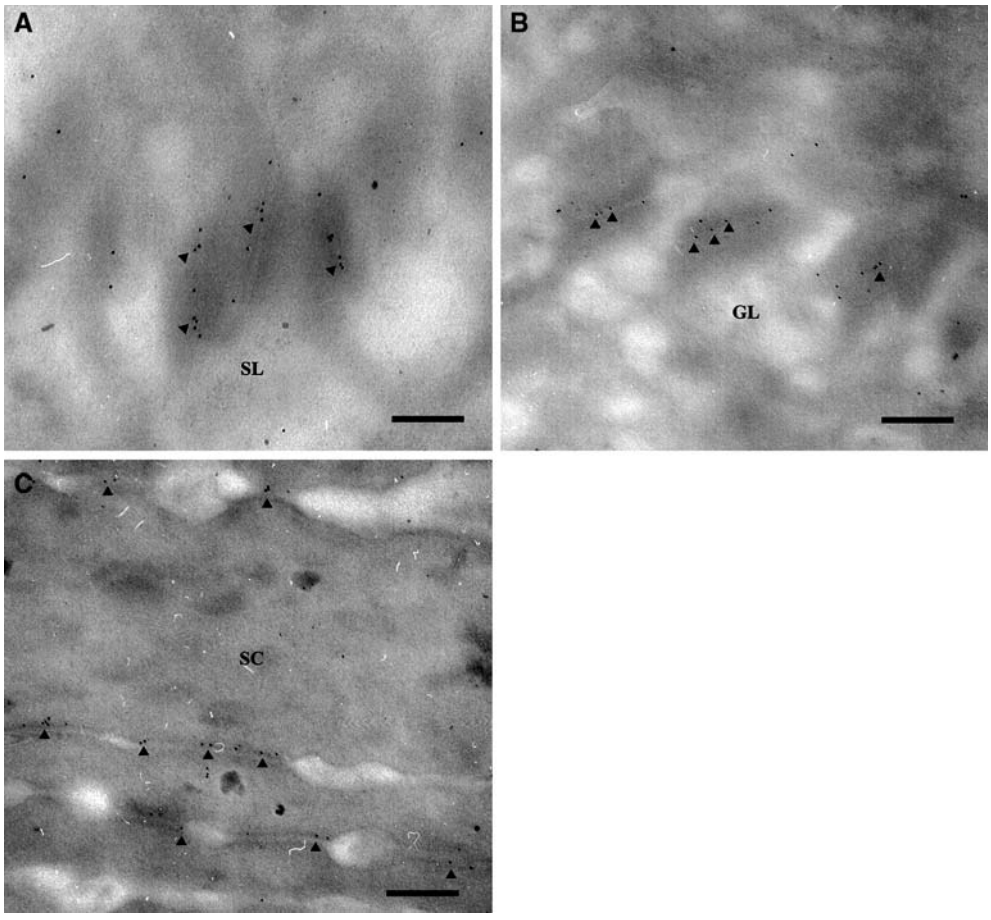

Fig. 4 Electron photomicrographs of Lowicryl ultrathin sections showing Dsg1 immunoreactivity in human keratinizing oral mucosa. Gold particles 10 nm. *Arrowheads* indicate immunolabelling. (**a**) spinous layer; (**b**) granular layer; (**c**) stratum corneum. Original magnification 15000X. Bar 285 nm. SL, spinous layer; GL, granular layer; SC, stratum corneum

antibody, Dsc1 and Dsg1 immunopositivity was detectable, respectively, on the intracellular and extracellular side of the junctions.

Human breast epidermis. Dsc1 and Dsg1 expression was not observed in the basal layer either in basal junctions, i.e. hemidesmosomes, or in lateral and apical junctions, i.e., desmosomes. An underevaluation of Dsg1 basal staining probably occurred as (i) not all epidermal desmosomes are Dsg immunoreactive and (ii) the basal layer was not always continuous in our ultrathin sections. Dsc1 immunolabelling was evident proceeding upwards in the spinous layer (Fig. 3a), increased towards the more superficial granular layer (Fig. 3b), and it completely disappeared in the stratum corneum (Fig. 3c). Dsg1 immunoreactivity appeared similarly distributed in all desmosomes of the suprabasal keratinocyte layers of living epidermis (Fig. 3d, e). Differently from Dsc1, Dsg1 expression was detected also in the corneodesmosomes (Fig. 3f). Immunolabelling for Dsg1 was always more abundant than for Dsc1 in the spinous and in the granular layer.

Human keratinizing oral mucosa. Dsc1 immunoreactivity was absent in the spinous layer, in the granular layer, and in the stratum corneum, as previously observed in immunofluorescence experiments. Dsg1 expression was evident in desmosomes between keratinocytes both in the upper spinous layer (Fig. 4a) and in the granular layer (Fig. 4b), without differences in labelling intensity. Similarly to epidermis, desmosomes between corneocytes were Dsg1-labelled (Fig. 4c). The pattern of Dsg1 distribution was almost comparable between KOM and epidermis, but the intensity of immunolabelling appeared lower in the oral epithelium.

DSC1 and DSG1 RT-PCR analysis

To ascertain if the immunoelectronmicroscopic observations were influenced by the antigen accessibility, Dsc1 and Dsg1 gene expression were investigated by RT-PCR analysis in epidermis and KOM. Our results confirmed that Dsc1 gene expression is exclusively detectable in epidermis (Fig. 5a), whilst Dsg 1 was evident both in epidermis and KOM (Fig. 5b). As expected, due to the lack of desmosomes, no amplification bands for both cadherins were detectable in fibroblasts (Fig. 6a, b).

Discussion

The present study demonstrates clearly and for the first time that desmocollin 1 (Dsc1) is not expressed in adult human keratinizing oral mucosa either at protein or

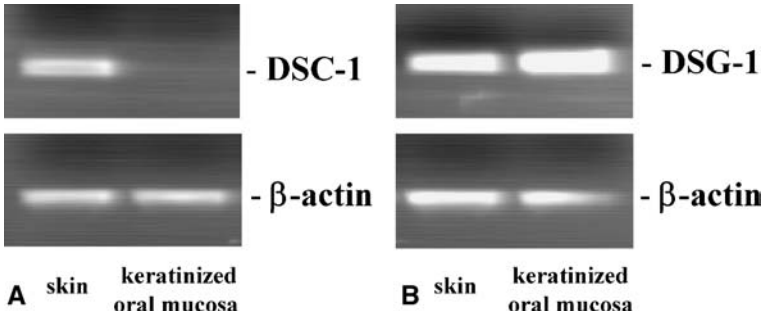

Fig. 5 RT-PCR analysis of Dsc1 (**a**) and Dsg1 gene expression (**b**) in human breast skin and human keratinizing oral mucosa. β-actin gene expression was utilized as a control gene

gene expression level. The coupling of molecular and morphological analysis for the expression of this desmosomal cadherin allowed us to exclude the fact that the negative Dsc1 immunoelectron microscopic results were due to antigen inaccessibility. By immunogold EM, desmoglein 1 (Dsg1) reactivity was lower in KOM than in epidermis, in accordance with previous immunoblot and immunofluorescence observations [27, 18]. Taken together, the present results strongly suggest an intrinsic regulation of adhesive properties in KOM and in epidermis.

The different molecular composition of desmosomes in these two stratified squamous keratinizing epithelia can be ultimately explained on the basis of the microenvironment to which they are exposed. Epidermis is dry, constantly exposed to changing humidities and temperatures lower than 37°C, whilst KOM is exposed to 100% humidity and mainly a temperature of 37°C and continuously undergoes heavy abrasion [23]. This mechanical stress results in a faster keratinocyte turnover [2] and a more frequent distribution of Ki67 in KOM than in epidermis [8].

During epithelial renewal, inter-keratinocyte adhesiveness plays a pivotal role. The lack of Dsc1 gene and protein expression in oral desmosomes can represent the molecular key underlying a weakened adhesion in this epithelium and allows oral keratinocytes to undergo a faster transition throughout the living layers of the epithelium. This hypothesis is based on the elegant observation that Dsc1 null mice displayed acantholysis [6], demonstrating the central role of Dsc1 in maintaining strong adhesion.

Whilst epidermal desmosomes are visible up to the stratum corneum, Dsc1 immunoreactivity rapidly and abruptly disappears concomitantly with keratinocyte terminal differentiation. Herein, inter-corneocyte adhesion is provided by corneodesmosomes [19]. As Caubet et al. [5] underlined in a recent paper, Dsc1 is one of the three components of the extracellular part of corneodesmosomes, but only fragments of this desmosomal cadherin have been observed in the stratum corneum of normal epidermis [12]. In our previous paper on Dsc1 expression and terminal differentiation in human hair follicle [7], we discussed the disappearance of immunoreactivity for Dsc1 in terminally differentiated keratinocytes on the basis of the proteolysis of cell–cell contacts during apoptosis [29]. In epithelial cells, it has been demonstrated that not only E and P cadherins [10, 26, 28], but also desmosomal proteins are efficiently cleaved by caspases or by metalloproteinases [29]. Thus, we can advance the hypothesis that, in our experimental conditions, Dsc1 maintains the proper structure to be identified by post-embedding electron microscopy in keratinocytes of the spinous layer and granular layer. In the stratum corneum, the residues of Dsc1 following the proteolysis, if present, cannot be revealed by using Dsc1-U100 clone.

Integrating (i) previous observations on intrinsic distribution of terminal differentiation markers [8], i.e. keratin 10, involucrin and loricrin, and (ii) our results on the different molecular composition of desmosomes in KOM and in epidermis, we propose that epidermal and oral keratinocytes might have a different phenotype relevant to withstand different stimuli present in specific microenvironments. Furthermore, a correlation between the histological appearance of the stratum corneum and Dsg3 distribution was reported in the epidermis and in KOM [1, 32] strengthening the hypothesis that the expression of desmosomal cadherins is not only differentiation-specific, but also tissue-specific. A potential

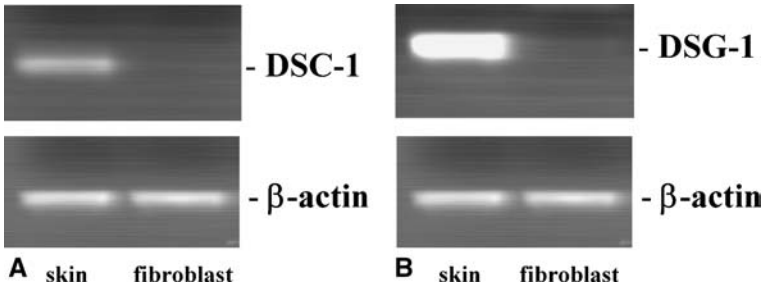

Fig. 6 Representative amplification of Dsc1 (**a**) and Dsg1 gene expression (**b**) in human breast skin and cultured fibroblasts. β-actin gene expression was utilized as a control gene

role of desmosomal cadherins as modulators of cellular phenotype is thus emerging [30].

The two major determinants of the different epithelial renewal in KOM compared to epidermis are: (1) higher rates of basal proliferation and (2) weakened adhesion underlying a faster keratinocyte passage throughout the epithelium. The present ultrastructural observations of a low Dsg1-mediated adhesion in oral corneocytes together with the lack of Dsc1 expression in KOM contribute to substantiate the latter mechanism.

Although further studies are needed to better define the spatial/temporal features of terminal differentiation in these epithelia, our work clearly indicates that adhesive needs and desmosomal composition are not comparable between adult keratinizing oral mucosa and epidermis and that this difference can account for the intrinsic specificity of a wide spectrum of keratinocyte features in each epithelium.

Acknowledgements We are indebted to Prof. Chiarella Sforza who carefully read this manuscript. We thank Mrs. Silvia Celon and Mr. Osvaldo De Negri for their skillfulness in performing immunofluorescence experiments and Mrs. Marianna Gaman and Mr. Luciano Losi for their excellent electron microscopy work.

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