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Extracellular matrix components of oral mucosa differ from skin and resemble that of foetal skin

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ABSTRACT

Objective: Wounds of both the oral mucosa and early-to-mid gestation foetuses have a propensity to heal scarless. Repair of skin wounds in adults, however, regularly results in scar formation. The extracellular matrix (ECM) plays an important role in the process of healing. The fate of scarless or scar forming healing may already be defined by the ECM composition, prior to wounding. In this study, the presence of several ECM components in oral mucosa (palatum) and skin was investigated.

Design: Immunohistochemical stainings of different ECM components were performed on skin, obtained from abdominal dermolipectomy surgery, and oral mucosa, derived after pharynx reconstruction.

Results: Expression of fibronectin, its splice variant ED-A, and chondroitin sulphate was elevated in oral tissue, whereas elastin expression was higher in skin. Tenascin-C, hyaluronic acid, biglycan, decorin, and syndecan-1 were expressed at similar levels in both tissues. Oral mucosa contained more blood vessels than skin samples. Finally, oral keratinocytes proliferated more, while dermal keratinocytes demonstrated higher differentiation.

Conclusions: Comparing ECM components of the skin and oral mucosa coincides with differences earlier observed between foetal and adult skin, and this might indicate that some ECM components are involved in the mode of repair.

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Abbreviations: α-SMA, alpha smooth muscle actin; ECM, extracellular matrix; fibronectin ED-A, fibronectin splice variant extra domain A; TGF-β, transforming growth factor-beta.

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1. Introduction

Wound healing can result in excessive scarring which is a great burden for patients.

Principally deep dermal wounds have the tendency to form hypertrophic scars, while superficial wounds heal with minimal scar formation. Dermal scar tissue differs in composition from normal skin as a result of excessive accumulation of extracellular matrix (ECM) components and a disturbed organization.[1] In addition, scars are less elastic and reach only about 70% tensile strength compared to intact skin.[2]

Contrary to skin wounds oral mucosal wounds heal faster, showing minimal scar formation. Thus far, exact mechanisms between scarless oral and scar forming dermal healing are unknown, although a few differences have been described. For instance, oral wounds contained lower number of immune cells.[3,4] As compared to dermal wounds reduced expression of the profibrotic factor transforming growth factor (TGF)-β1 was found in oral wounds, while antifibrotic TGF-β3 was elevated.[5,6] Finally, oral mucosa fibroblasts proliferated faster than the dermal counterparts.[7] In healthy tissue oral fibroblasts produced significantly more hepatocyte growth factor and keratinocyte growth factor, compared to dermal fibroblasts.[8] Contraction was enhanced in oral fibroblasts, although these cells appeared to be less susceptible to TGF-β1 with respect to alpha smooth muscle actin expression (α-SMA).[9]

Scarless healing is also observed in early-to-mid gestational foetal wounds. Fast reepithelialization, lack of immune mediators and complete regeneration are typical features of foetal wound repair.[10] Studies that investigated the mechanism of scarless healing mainly focused on processes during wound healing, though the fate of scarless or scar forming healing may already be found in the tissue architecture itself, prior to wounding. Coolen et al.[11] demonstrated increased expression of the ECM components fibronectin and chondroitin sulphate in foetal skin, while elastin was only present in adult skin.

The ECM plays a significant role in cell adherence, migration, proliferation and it directs cell phenotype. Therefore differential expression of ECM components may possibly contribute to scar forming or scarless repair. The ECM comprises proteoglycans (e.g. heparan sulphate, chondroitin sulphate, keratan sulphate), fibrous proteins (collagens, elastin, fibronectin, laminin), and functions as a reservoir for growth factors. ECM proteins are synthesized and secreted by fibroblasts and myofibroblasts. When comparing oral and dermal fibroblasts, several differences were found regarding ECM expression. For instance, hyaluronan synthase-3 was highly expressed by oral fibroblasts, but expression by dermal fibroblasts was low.[12] On the contrary, hyaluronan synthase-1 was expressed in dermal fibroblast while it was absent in oral fibroblasts. The oncofetal cytokine migration stimulating factor, which is a truncated form of fibronectin, was only produced by oral (gingiva) and foetal fibroblasts but not by healthy adult dermal fibroblasts.[13,14] This cytokine stimulates migration of fibroblasts, epithelial cells and endothelial cells, but also promotes angiogenesis and hyaluronic acid synthesis.[15] These data may imply an elevated hyaluronic acid expression in the oral mucosa, though a study by Pedlar[16] showed increased hyaluronic acid expression only in the palatum, when compared to the rat skin or gingiva. Also matrix metalloproteinases (MMPs) were shown to be differentially expressed: oral fibroblasts produced more MMP-2 and -3 compared to their dermal counterparts.[17,18] In foetal fibroblasts, an increased gelatinase activity was reported in contrast to adult fibroblasts, indicative for reduced collagen accumulation.[19]

Additionally, several ECM components were shown to be associated with the formation of fibroproliferative disorders. For example, mice deficient for the fibronectin splice variant extra domain A (ED-A), did not develop pulmonary fibrosis after challenge with a fibrotic agent.[20] On the contrary, fibronectin ED-A has been shown to be important for repair by means of participation in the reepithelialization process.[21] Levels of the small leucine-rich proteoglycan biglycan was significantly elevated in hypertrophic scars, compared to normal skin.[22] Expression of decorin and fibromodulin however, was lower in these scars. Addition of recombinant decorin downregulated cell proliferation, TGF-β1 production, and collagen synthesis in hypertrophic scar fibroblasts.[23]

In this study, we evaluated the location and deposition of several ECM components in skin and oral mucosa, as expression of various ECM components might be involved in the fate of healing.

2. Materials and methods

2.1. *Tissue samples*

Human skin was obtained from six healthy individuals (gender not registered, mean age 37 ± 18 years old) undergoing abdominal dermolipectomy. All donors provided informed consent according to institutional and national guidelines. Skin pieces of maximal 1 cm^2 were embedded in Tissue Tek® OCT™ Compound (Sakura Finetek, Alphen aan den Rijn, The Netherlands) and stored at −80 °C until sectioning. Oral mucosa was obtained after informed consent from six patients (5 females, one male; mean age 6 ± 3 years old) with a history of open cleft palate undergoing pharynx reconstruction. A small part of the palate was resected and processed as described for human skin. To overcome discrepancies due to age, we tested oral mucosal tissue from one male aged 27 years old (informed consent), and found identical results as with oral tissues derived from juveniles (data not shown).

2.2. *Immunohistochemistry*

Skin and oral mucosal cryosections (5 μm) were mounted on collagen coated glass slides and fixed in acetone for 10 min. Peroxidase was quenched with H_2O_2 and sections were incubated with primary antibodies (Table 1) for 1 h at room temperature. Subsequently, sections were incubated with Envision (Dako, Glostrup, Denmark) and detection was performed using diaminobenzidine (DAB) as chromogen substrate (Dako). Finally, sections were counterstained with haematoxylin, dehydrated in ethanol and embedded in

Table 1 – Antibodies used for immunohistochemistry.

Antibody	Clone	Host	Isotype	Dilution	Source
a-SMA	1A4	Mouse	IgG2a	1:100	Abcam
Biglycan		Mouse	IgG2a	1:300	Abcam
CD31	JC70A	Mouse	IgG1	1:50	Dako
Collagen I		Mouse	IgG1	1:800	Abcam
Collagen III		Mouse	IgG1	1:400	Abcam
Chondroitin sulphate	CS-56	Mouse	IgM	1:500	Sigma–Aldrich
Decorin		Mouse	IgG2b	1:300	Abcam
Elastin	BA-4	Mouse	IgG1	1:500	Sigma–Aldrich
Fibronectin	Polyclonal	Rabbit	IgG	1:1200	Sigma–Aldrich
Fibronectin ED-A	IST-9	Mouse	IgG1	1:100	Sirius Biotech
Hyaluronic acid	Polyclonal	Sheep	IgG	1:200	Abcam
Involucrin	SY5	Mouse	IgG1	1:1000	Novocastra
Ki-67	MIB-1	Mouse	IgG1	1:50	Dako
Syndecan-1	DL-101	Mouse	IgG1	1:50	eBioscience
Tenascin-C	Polyclonal	Rabbit	IgG	1:100	Millipore/Chemicon

entellan (Merck Millipore, Darmstadt, Germany). Negative controls were conducted by use of non relevant isotype control antibodies.

2.3. *Data analysis*

The staining was microscopically evaluated in all samples, by means of a visual score ranging from low to high intensity. Classification was defined as negative (0), weakly positive (1), moderate positive (2), largely positive (3), or intensely positive (4). The scoring was determined for the epidermis/epithelium, basement membrane (BM) and dermis/lamina propria, of which the latter was divided in the papillary and reticular layer. A representing delineation for these different layers is depicted in Fig. 1.

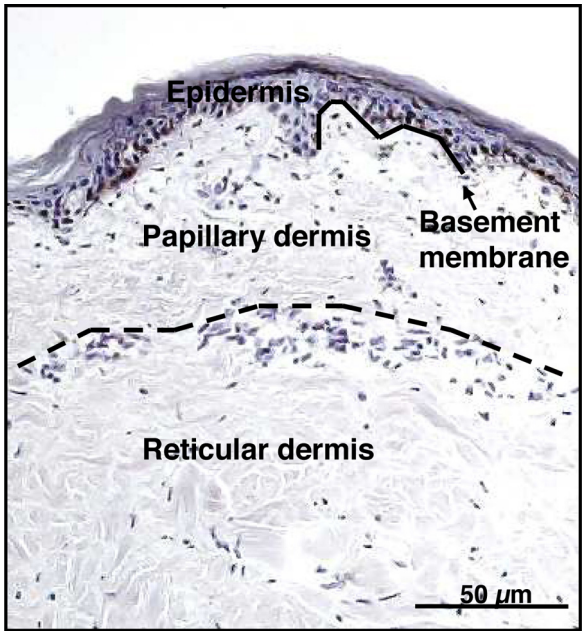

Fig. 1 – Histological skin section showing delineations of different layers. Example of a skin section representing delineation of the following layers: epidermis, basement membrane, papillary dermis and reticular dermis.

2.4. *Statistical analysis*

The scoring procedure was independently conducted by two investigators. Statistical significance was determined by Mann–Whitney *U* test analysis using Graphpad Prism software (GraphPad Software Inc., San Diego, USA). $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$.

3. Results

3.1. *Several ECM components differ between skin and oral mucosa*

First, presence of collagen type I and III was compared between oral and dermal tissue. Collagen type I was equally expressed in both tissues and the same results were found for collagen type III expression; no differences were observed between both tissues (Fig. 2A and B). Fibronectin and chondroitin sulphate were more expressed in oral tissue than skin, while elastin was prominently found in the skin, but at low levels in the oral mucosa (Fig. 3A and B).

Several ECM components are known to be upregulated during regeneration such as wound healing or malignancies. Among these are fibronectin ED-A, tenascin-C and hyaluronic acid. The oral tissue had an increased expression of fibronectin ED-A, as compared to the dermis (Fig. 4A and B). Tenascin-C and hyaluronic acid were not differently expressed between the two types of tissue (Fig. 4A and B).

Next, a group of ECM components (biglycan, decorin, syndecan-1) related to fibrosis was evaluated. Biglycan and decorin were not differently expressed between dermal and oral tissue (Fig. 5A and B). Syndecan-1 expression was equally expressed in the dermis and/or basement membrane between skin and oral tissue (Fig. 5A and B). Skin keratinocytes however, had increased expression of this protein compared to oral keratinocytes (Fig. 5A and B). Syndecan-1 was mainly expressed in the basal layer of the skin epidermis.

3.2. *More blood vessels in oral tissue*

To find out whether unaffected oral tissue already contains reduced numbers of blood vessels, their presence was

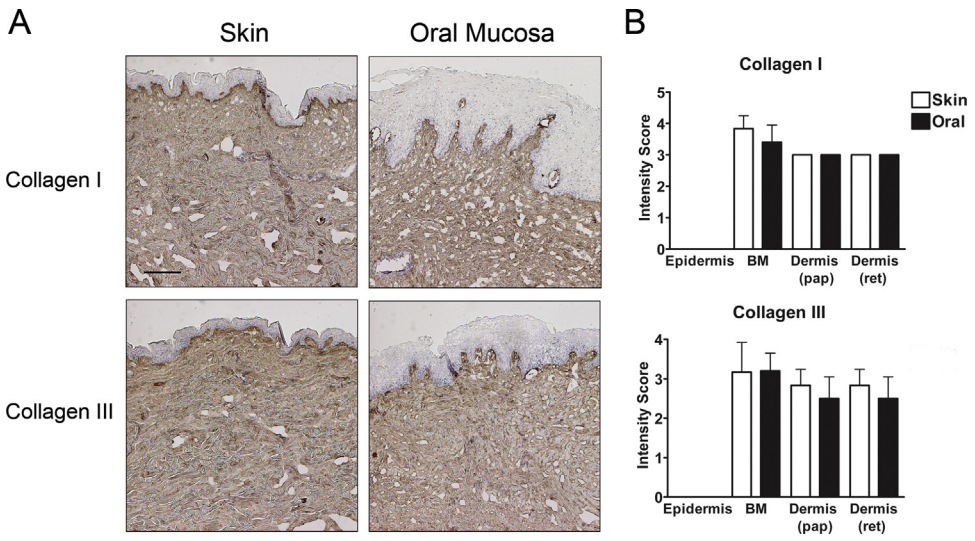

Fig. 2 – Collagen type I and III in skin and oral mucosa. (A) Immunohistochemical localization of collagen type I and III. (B) Staining intensity was quantified for all layers of skin and oral mucosa; the epidermis, basement membrane (BM), papillary (pap) and reticular (ret) part of the dermis/lamina propria. Data represents the average scoring and SD (n = 12). Scale bar: 50 μm.

determined by CD31 and α-SMA staining. Expression of CD31 was significantly higher in the reticular lamina propria, as compared to the dermis (Fig. 6A and B). α-SMA expression was also higher in the oral tissue, although only apparent in the papillary area.

3.3. *Increased proliferation in oral, but higher differentiation in dermal keratinocytes*

Finally, proliferation and differentiation was investigated by detecting Ki-67 and involucrin, respectively. A small number

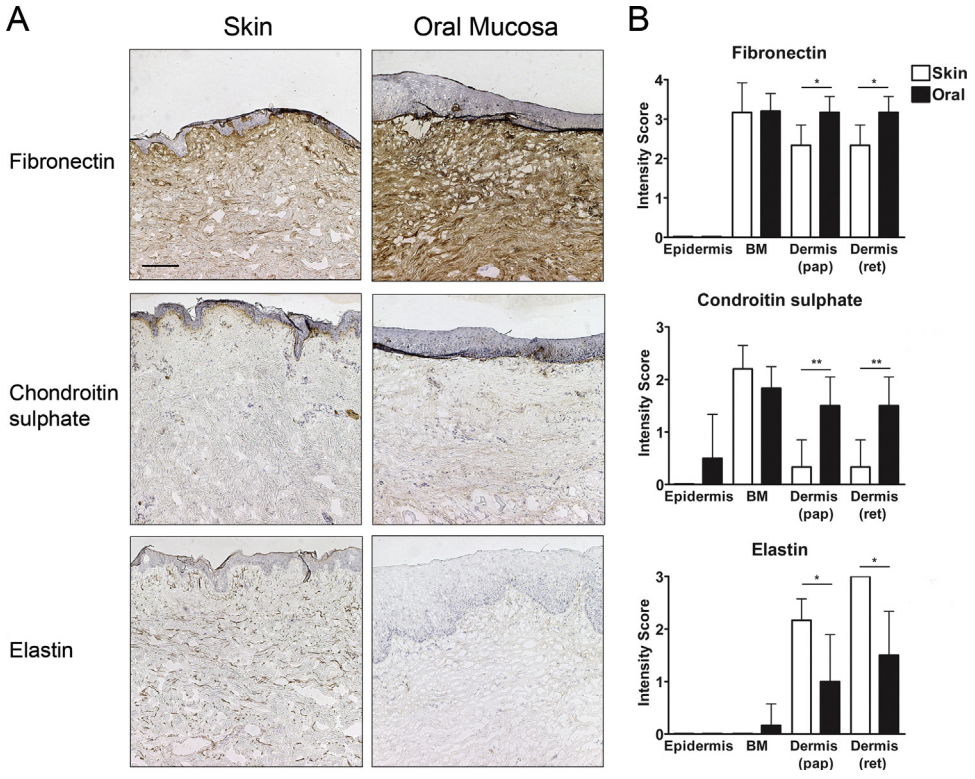

Fig. 3 – Fibronectin, chondroitin sulphate, and elastin in skin and oral mucosa. (A) Immunohistochemical localization of fibronectin, chondroitin sulphate, and elastin. (B) Staining intensity was quantified for all layers of skin and oral mucosa; the epidermis, basement membrane (BM), papillary (pap) and reticular (ret) part of the dermis/lamina propria. Data represents the average scoring and SD (n = 12). Scale bar: 50 μm.

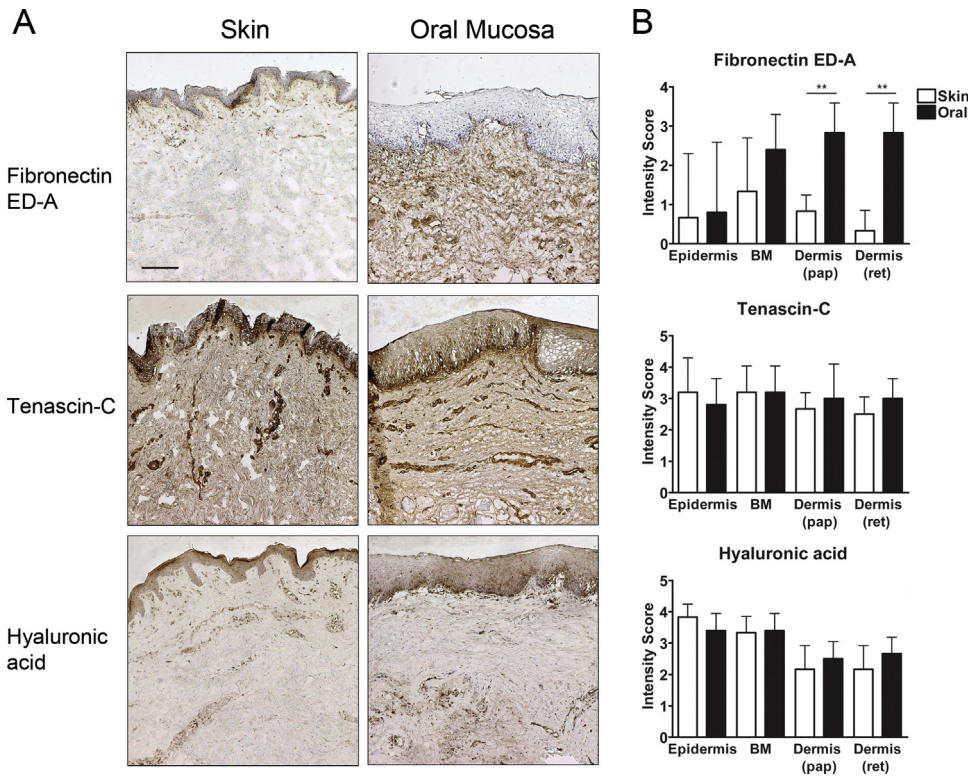

Fig. 4 – Fibronectin ED-A, tenascin-C, and hyaluronic acid in skin and oral mucosa. (A) Immunohistochemical localization of fibronectin ED-A, tenascin-C, and hyaluronic acid. (B) Staining intensity was quantified for all layers of skin and oral mucosa; the epidermis, basement membrane (BM), papillary (pap) and reticular (ret) part of the dermis/lamina propria. Data represents the average scoring and SD (n = 12). Scale bar: 50 μm.

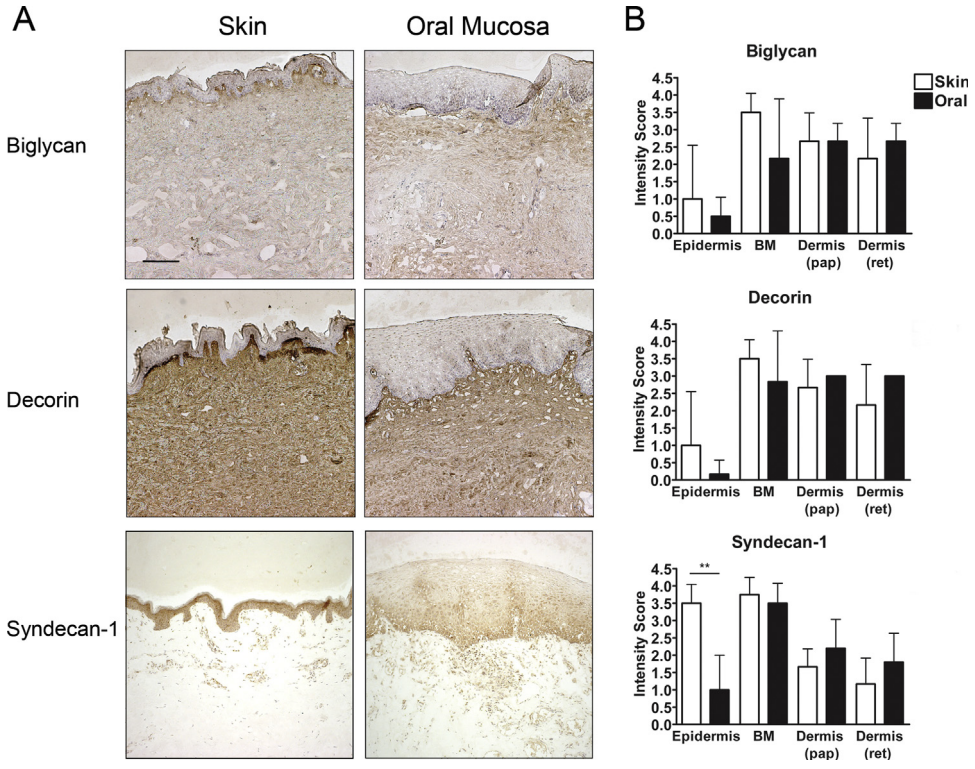

Fig. 5 – Biglycan, decorin, and syndecan-1 in skin and oral mucosa. (A) Immunohistochemical localization of biglycan, decorin and syndecan-1. (B) Staining intensity was quantified for all layers of skin and oral mucosa; the epidermis, basement membrane (BM), papillary (pap) and reticular (ret) part of the dermis/lamina propria. Data represents the average scoring and SD (n = 12). Scale bar: 50 μm.

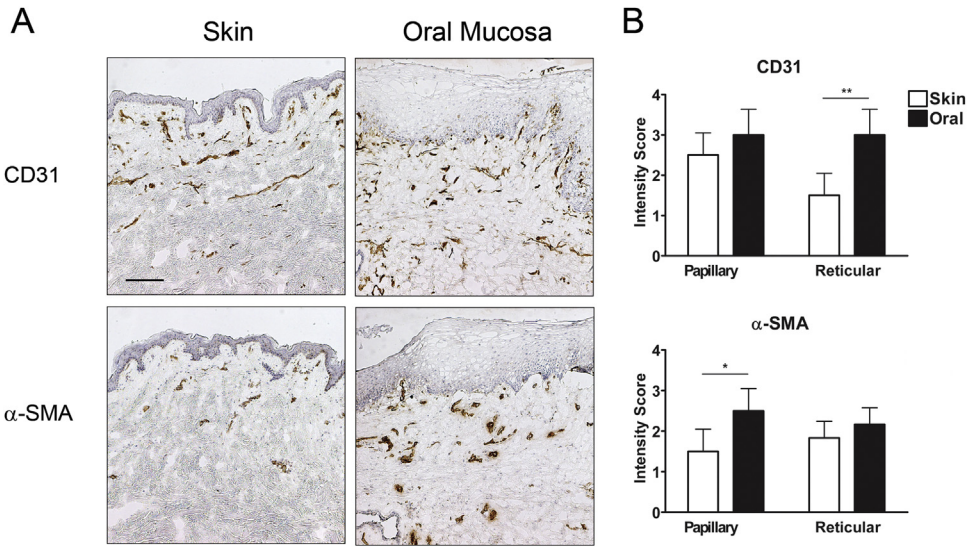

Fig. 6 – Localization of blood vessels in skin and oral mucosa. (A) Blood vessels were visualized by means of CD31 and α-smooth muscle actin (SMA) staining. (B) Staining intensity was quantified for the papillary (pap) and reticular (ret) layer of the dermis/lamina propria. Data represents the average scoring and SD (n = 12). Scale bar: 50 μm.

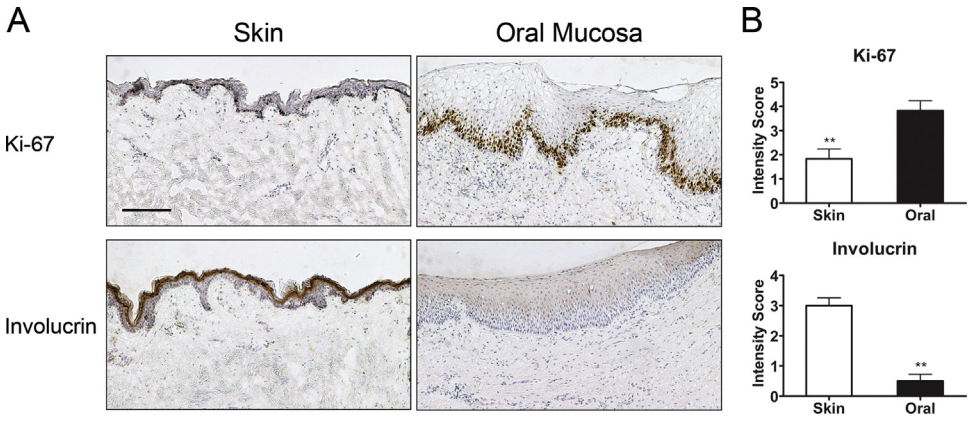

Fig. 7 – Keratinocyte proliferation and differentiation in skin and oral mucosa. (A) Proliferation was determined by Ki-67 staining and differentiation by involucrin. (B) Quantification of the staining. Data represents the average scoring and SD (n = 12). Scale bar: 50 μm.

of Ki-67 positive cells were present in skin, but the oral tissue had visibly enhanced numbers of Ki-67 positive cells (Fig. 7A and B). The oral epithelium had multiple layers of cells undergoing proliferation, while in the epidermis only one proliferating layer was observed. Involucrin is an elementary component of the cornified envelop, being synthesized in the suprabasal epidermal layers.[24] Involucrin was significantly expressed in the granular layer of the epidermis, while the expression was remarkably lower in the oral epithelium (Fig. 7A and B).

4. Discussion

In this study the presence of several ECM components and other structures in the skin and oral mucosa was investigated. A previous study showed differences in the expression of ECM components between foetal and adult skin, and remarkably, the same pattern was found in our present study comparing oral and dermal tissue.[11] Fibronectin, fibronectin ED-A, and chondroitin sulphate were more expressed in oral mucosa in contrast to skin, while the reverse was found for elastin. One of the explanations for reduced elastin expression might be that the elastic fibres oxytalan and elaunin are more prominent in the oral mucosa as compared to skin.[25] Both oxytalan and elaunin consists of fibrillin microfibrils, although elastin is only incorporated in small quantities in elaunin fibrils.[26] Oxytalan fibres are expressed in tissues subjected to mechanical stress, and have a similar role as elastin.

With respect to chondroitin sulphate, rabbit palatal fibroblasts increased cell adhesion and proliferation when cultured in the presence of this protein.[27] In addition, silencing

chondroitin sulphate synthase 1 in human fibroblasts reduced the expression of caspase 1, which is important for Langerhans cell migration, and inflammation.[28] These data suggest that high expression of chondroitin sulphate during both oral and foetal wound repair might be responsible for fast wound closure observed in these two tissues.

The glycoprotein fibronectin is important in wound healing, since it provides attachment sites for fibroblasts and epidermal cells. Application of fibronectin to rat wounds increased the reepithelialization rate, as well as fibroblast and macrophage migration.[29] This underlines an association between high fibronectin expression and enhanced wound repair observed in oral wound healing.

The fibronectin splice variant ED-A was shown to be essential for wound healing but is also enhanced in lung fibrosis.[20,21] In the oral mucosa, fibronectin ED-A expression was higher compared to skin. Elastin on the contrary, was virtually absent in the oral mucosa (palatum), although in non-keratinized areas of the oral mucosa elastin was shown to be present.[30] Collagen I and III, hyaluronic acid, and tenascin-C were equally expressed in both human skin and oral mucosa, although in animals tenascin-C (in pig) and hyaluronic acid (in rat) were elevated in oral tissues when compared to skin.[16,31] Based on these data, it remains unclear whether these ECM components may really play a role in appropriate wound healing.

Biglycan and decorin expression did not differ between oral mucosa and skin. Expression of biglycan is regulated by the TGF-β pathway via intracellular SMADs.[32] Biglycan is upregulated in hypertrophic scars, where TGF-β expression is enhanced. Decorin plays a role in the control of collagen fibril assembly and regulates TGF-β activity by binding it.[33,34] Decorin expression is reduced in hypertrophic scars, which may explain the enhanced TGF-β expression in these scars. De- or increased expression of these proteins during aberrant wound repair is therefore more likely to be a consequence of other repair processes such as the TGF-β pathway.

The cell surface proteoglycan syndecan-1 mediates cell binding to the ECM, and is associated with cardiac fibrosis.[35] Its expression was increased in epidermal keratinocytes compared to oral counterparts. Furthermore, syndecan-1 is expressed in differentiating keratinocytes, which is in line with the increased expression of involucrin found in epidermal keratinocytes. Mice overexpressing syndecan-1 showed increased epidermal hyperproliferation, and cell proliferation and reepithelialization was decreased during wound healing, compared to wild type mice.[36] Our Ki-67 data shows that keratinocyte proliferation was enhanced in oral mucosa, a phenomenon also observed during wound healing, where reepithelialization occurs faster than in dermal wounds.[4,6] These results are somewhat predictable since it is already known that oral epithelial cells are much less differentiated and show enhanced turnover, compared to skin keratinocytes. Nevertheless, a higher proliferation capacity and reduced differentiation potential of oral keratinocytes underline that fast reepithelialization might contribute to reduced scar formation.

We observed more blood vessels in the oral mucosa than in skin tissue, and similar results were found in a mouse study.[37] In the reticular layer of the oral mucosa, more CD31 positive blood vessels were found, while in the papillary part more α-SMA positive blood vessels were present. Based on these results it seems that small vessels reside in the reticular and larger ones in the papillary layer of the oral mucosa.

A limitation of our study could be that skin and oral mucosa were not derived from the same donor, this would have been ideal. In addition, skin was obtained from adult individuals while oral mucosa was derived from juveniles. It is difficult to obtain adult human oral mucosa, although we had excess to one adult donor. To avoid that ECM-differences found between skin and oral mucosa is age-related, the same staining procedure was applied to this donor. Here, identical observations were found as with juvenile oral tissue.

To conclude, differences in the distribution of a number of ECM components were comparable to that seen between foetal and adult skin. Our data emphasizes similarities between oral and foetal tissue, which eventually might play a role in the mode of healing, which is comparable between these two tissues.

Contributors

Judith Glim constructed the study, performed the data analysis and drafted the manuscript. Vincent Everts and Frank Niessen guided the study, and project coordination was performed by Magda Ulrich and Robert Beelen. Tissue material was, amongst others, mainly provided by Frank Niessen.

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Competing interests

None of the authors have any financial or other conflict of interest.

Ethical approval

None declared.

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