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RESEARCH

Stromal Expression of CD34, α-Smooth Muscle Actin and CD26/DPPIV in Squamous Cell Carcinoma of the Skin: A Comparative Immunohistochemical Study

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Abstract Invasion pathogenesis is one of the most complicated issues in the literature. There are numerous studies concerning the tumor markers implicated in the preinvasive-invasive tumor sequence. Despite ample studies on the invasion pathogenesis of cutaneous melanomas, there is limited and dispersed work presently available on non-melanoma skin cancer. The vast knowledge in the literature concerning this issue in squamous cell carcinoma comes mostly from the studies of the oral cavity, esophagus, larynx, and cervix. In this study, we investigated tumor-free neighboring stroma and tumor stroma in squamous cell carcinomas (SCCs) of the skin as well as keratoacanthomas (KAs) with respect to the presence of stromal CD34-positive (CD34+) fibrocytes and α-smooth muscle actin-positive (α-SMA+) myofibroblasts using seborrheic keratosis (SKs) and non-tumoral skin samples as controls. We also evaluated the stromal expression pattern of CD26/DPPIV (CD26), a tumor suppressor gene product that also has immunoregulatory properties. Immunohistochemistry was performed on samples of 31 SCC, 8 KA, 15 SK and 10 non-tumoral skin samples. Peri-tumoral stroma from resection margins was also evaluated. We found that CD34 and α-SMA demonstrated significantly different staining between benign and malignant squamous skin lesions consisting of a loss of CD34+ fibrocytes paralleled by a gain of α-SMA+ myofibroblasts in malignant tumor stroma. Additionally, it was shown that CD26 expression was lower in tumor stroma when compared to that of tumor neighboring stroma. However, we concluded that this finding may be attributable to the solar elastosis areas in the peritumoral tissue, which shows diffuse strong positivity for this marker.

Keywords CD34 · α-SMA · CD26 · Squamous cell carcinoma · Tumor stroma

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Abbreviations

α-SMA	α-Smooth Muscle Actin
CD26	CD26/DPPIV
SCC	Squamous Cell Carcinoma
KA	Keratoacanthoma
SK	Seborrheic Keratosis
TMS	Tumor Stroma
NTMS	Non-Tumoral Stroma (peritumoral stroma)
HPF	High Power Field

Introduction

There is increasing evidence that stromal reaction in cancer has an important diagnostic and prognostic significance. Recent studies have shown that CD34+ stromal cells and myofibro-

blasts may play an important role in host response to invasive cancer [1]. During progression to invasive carcinoma, tumor cells activate the underlying stromal cells and generate phenotypically altered tumor stroma, which cooperates with cancer cells to promote tumor progression [2]. Tumor stroma provides a scaffold for tumor cells and microvasculature allowing transport of interstitial fluid carrying nutrients. It may also limit the influx of inflammatory cells, thus providing protection from the host immune system [3].

With respect to their cellular composition, tumor-laden and tumor-free stroma are clearly distinct. These differences are widely independent of the anatomical site and histological type of carcinoma and consist of a loss of CD34+ fibrocytes and a subsequent gain of α-smooth muscle actin (SMA) + myofibroblasts [4–10]. CD34+ fibrocytes appear to be constitutive elements of the connective tissue in a multitude of anatomical sites, such as the skin, breast, gastrointestinal tract, and cervix. In all of the aforementioned locations, the stroma of invasive carcinomas discloses a reduction or complete loss of CD34+ fibrocytes paralleled by the occurrence of α-SMA+ myofibroblasts [5–10].

CD26 plays an important role in tumor biology, and is useful as a marker for various cancers, with its levels either on the cell surface or in the serum being increased in some neoplasms and decreased in others [11, 12]. Previous studies have extensively described the role of CD26 in regulating inflammatory and immunological response, apoptosis and in cleaving its substrates such as chemokines and cytokines [12]. More recent studies focused mostly on the function of CD26 in extracellular matrix degradation and angiogenesis, processes that lead to an increase in tumorigenicity and development of metastases [11, 13–16]. Due in part to its ability to regulate the activity of biopeptides, it can act as a tumor suppressor or activator [11]. Despite the contradictory findings showing CD26 as both a tumor suppressor and promoter [15–19], it can be assumed that CD26, either alone or in complexes with other serine proteases, is strongly related to tumor invasion and development of metastases [20].

CD26 has been investigated in several different cancer tissues, but to date and to our knowledge, not yet in skin squamous cell cancer (SCC). We undertook the present study to analyze the stroma and the tumor-free stroma in SCCs, keratoacanthomas (KAs) and seborrheic keratosis (SK) of the skin with respect to the presence or absence, respectively, of CD34+ fibrocytes and α-SMA+ myofibroblasts. We additionally investigated whether stromal cells express the CD26 antigen.

Materials and Method

This study comprises a total of 31 SCCs of the skin obtained from 21 patients, 13 of whom were male (age range: 41–85 years; arithmetic mean: 68 years) and 8 KAs (5 male, 3 female, median age: 63). The SCC samples were selected among the overtly infiltrating cases from various locations (6 face, 3 scalp, 3 ear, 1 lip, 1 foot, 1 hand). Localization was not available in 4 patients. The stroma beyond the border of the tumor, regarded as tumor-free tissue from resection margins, was available for comparison. The control group consisted of 16 cases of SK (9 male, 7 female, median age: 60) and 11 samples of non-tumoral skin (7 male, 4 female, median age: 43). Non-tumoral skin samples were selected from mammary reduction, pilonidal sinus materials and non-inflammatory skin samples biopsied for other reason. Cases were selected retrospectively from the archives of Yildirim Beyazit Research and Training Hospital, Pathology Department.

Immunohistochemistry was performed with a peroxidase-streptavidin method on formalin-fixed paraffin-embedded tissue using standard protocols. CD26 antigen retrieval was performed by using a microwave pre-treatment by heating the deparaffinized and rehydrated sections, immersed in sodium citrate buffer (pH=6.0). For the α-SMA and CD34 no antigen retrieval was performed according to the datasheet instructions. Immunophenotyping of samples used 1:100 mouse anti-CD26 (Abcam, clone ab28340, Cambridge, MA, USA), 1/400 mouse anti-CD34 (Thermoscientific, clone QBEnd-10, Fremont, CA, USA) and 1/800 mouse anti-α-SMA (Thermoscientific, clone 1A4, Fremont, CA, USA).

We analyzed the expression and distribution of CD34+ and α-SMA+ stromal cells in the tumor stroma and peritumoral tissue of SCC and KA. CD34 stained both dendritic stromal cells and endothelial cells whereas α-SMA immunostaining was restricted to perivascular cells and stromal cells. Endothelial and sebaceous gland positivity was used for internal controls in case of CD26.

Semiquantitative Analysis

Expressions in stromal cells in tumoral and non-tumoral tissue were semi-quantified using a visual grading system in which the staining intensity was categorized into four groups as: 0, 1+, 2+, 3+, where group 0 was defined as having no positive staining. Groups 1–3 were defined as groups with positive staining of increasing intensity compared to positive control (<25%: 1+, 25–50%: 2+, >50%: 3+) [20].

Evaluation of Chronic Inflammation

The mononuclear cell infiltration was also graded semi-quantitatively as follows: <10 mononuclear cells/HPF (400X): grade 1, ≥10 mononuclear cells/HPF(400X): grade 2 (patchy infiltration without lymphoid follicles), ≥10 mononuclear cells/HPF(400X) with dense continuous infiltration and/or lymphoid follicles: grade 3. At least 10 HPF

were evaluated for each sample and patchy or continous infiltration pattern on low power was also checked.

Statistical Analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 11.5 software (SPSS Inc., Chicago, IL, USA). Data were expressed as median (minimum-maximum). The median differences regarding degrees of expression among groups were evaluated by Kruskal-Wallis test. When the *p*-value from the Kruskal-Wallis test statistics was statistically significant, multiple comparison test was used to to determine stepwise differences between groups. Bonferroni-adjusted Wilcoxon signed rank test was applied for the intragroup comparisons. The associations between degrees of inflammation and expressions were analyzed by Spearman's correlation test. A *p*-value less than 0.05 was considered statistically significant. The Bonferroni Correction was applied for controlling type I error in all possible multiple comparison test.

Results

Staining Results for α-SMA, CD34 and CD26

The staining degrees for the complete immune panel of all cases are shown in Table 1 and Fig. 1.

Intergroup Differences for the Markers

With respect to staining degrees of tumoral stroma in SCC, KA, SK and non-tumoral skin samples, multiple intergroup statistical analyses were done. No statistically significant difference was observed in staining degrees of the three markers between benign groups (non-tumoral skin samples and SK) and malignant groups (KA and SCC). However, there was a statistically significant different staining for α-SMA and CD34 between benign groups (non-tumoral skin samples and SK) and SCC. KA showed no significantly different staining pattern from SCC or benign groups, except for the CD34 staining in the tumor stroma when compared with that of SK. The results were much more varied for CD26: the only significant difference was between SK and SCC for this marker ($p<0.001$).

Expression Differences Between Tumoral and Peritumoral Stroma

Multiple analyses were done with respect to the staining degrees of all the markers in the tumor stroma and peritumoral subepithelial tissue in KA and SCC groups (Fig. 2). We found no statistically significant difference for the KA group between tumoral stroma and peritumoral stroma, which can also be attributed to the insufficient number of cases in this group. The results were more coherent in the SCC group: there was a significantly different staining between tumoral stroma and the neighboring non-tumoral stroma for all of the markers (Wilcoxon signed rank test, according to the Bonferroni correction; $p<0.0083$ was accepted as statistically significant) (Figs. 3, 4, 5a,b and 6a,b). These tumor margins showed basically atrophic type solar keratosis in 17 patients in the SCC group. Additionally, 13 patients had solar elastosis in the peritumoral tissue. It was noted that there was a diffuse strong positivity for CD26 in the solar elastosis fields in the neighboring stroma (Fig. 7).

Comparisons Between Markers for the Tumoral and Peritumoral Stroma

Multiple statistical analyses between markers were done with respect to the staining intensities for the tumoral stroma and non-tumoral neighboring stroma in KA and SCC groups. We found a statistically significant difference between SMA and CD34 in the non-tumoral tissue in the SCC group. No other significant relation was found for the tumoral and non-tumoral stroma between the various groups of markers (Wilcoxon signed rank test, according to the Bonferroni correction; $p<0.0042$ was considered as statistically significant).

Evaluation of Staining Degrees Between Benign and Malignant Groups

There was a statistically significant different staining pattern for all markers between the benign and malignant groups (non-tumoral skin samples + SK/KA + SCC) ($p<0.001$).

Table 1 Evaluation of the stromal antigen expression for α-SMA, CD34 and CD26 [the data are shown as median (minimum-maximum)] (*tumor stroma) (**tumor margin)

Groups	Number of samples	α-SMA	CD34	CD26
Non-tumoral skin	10	0 (0–1)	2 (1–3)	2 (0–3)
Seborrheic keratosis*	15	0 (0–0)	3 (1–3)	2 (1–3)
Keratoacanthoma*	8	1 (0–2)	0 (0–2)	1 (0–3)
Squamous cell carcinoma*	31	1 (0–3)	0 (0–2)	0 (0–2)
Peritumoral tissue from SCC **	31	0 (0–1)	2 (0–3)	2 (0–3)
p		<0,001	<0,001	<0,001

	α-SMA	CD34	CD26
Non-tumoral skin samples	0.000	2.000	2.000
Seborrheic keratosis	0.000	3.000	2.000
Keratoacanthoma	1.000	0.000	1.000
SCC	1.000	0.000	0.000

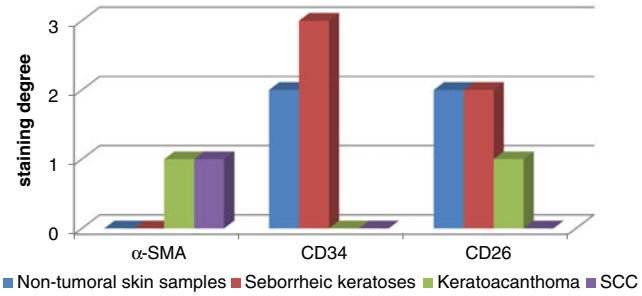

Fig. 1 Staining degrees of the markers in different study groups. Note that α-SMA and CD34 expressions significantly differ between the benign and malignant groups

Correlation Between Staining Degrees and Inflammation

There was no statistically significant relation between severity, presence and absence of inflammation and staining degree of the markers in KA and SCC ($p<0.0042$).

Discussion

Cancer research has traditionally focused on the alterations within genetically transformed cancer cells. In recent years, however, tumors have been increasingly perceived as complicated unorganized organs that, in addition to the cancer cells, also contain various stroma cells, such as

	Keratoacanthoma			SCC		
	SMA	CD34	CD26	SMA	CD34	CD26
TMS	1	0	1	1	0	0
NTMS	0	2	3	0	2	2

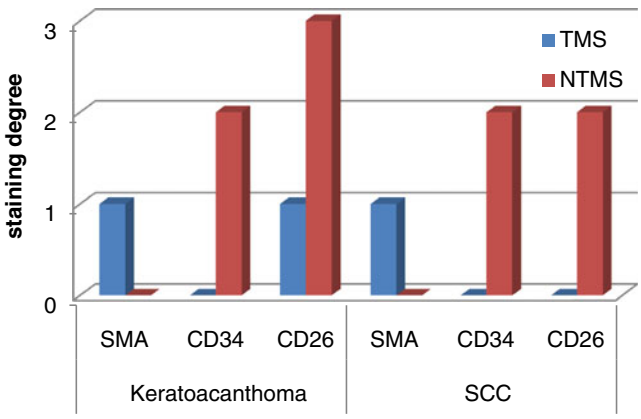

Fig. 2 Staining degrees of the markers in KA and SCC groups in the tumor stroma (TMS) and the neighboring non-tumoral stroma (NTMS)

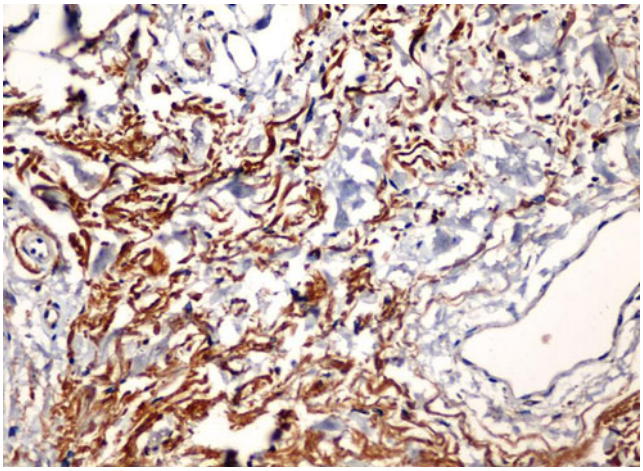

Fig. 3 CD26 staining in the peritumoral stroma in SCC; strong positivity of the fibrocytes and the collagen (tumor margin, x40)

endothelial cells, immune cells, and fibroblasts [1, 21, 22]. Stromal cells influence many aspects of tumor development including inception, growth, angiogenesis, local invasion, and metastasis [1–3, 6–10, 22–24].

Although it is widely accepted that fibroblasts facilitate tumor progression, the origin(s) of such activated fibroblasts are largely unknown. The cells of origin of myofibroblasts as well as the mechanisms that trigger their formation are not yet completely understood. Activation and proliferation of resident tissue fibroblasts contribute to fibroblast accumulation in the tumor microenvironment [25]. It has been suggested that they might be derived from CD34+ dendritic cells, smooth muscle cells or pericytes [26]. Recent studies also point to a possible origin of carcinoma-associated fibroblasts from the bone marrow. Moreover, periadventitial cells are implicated as sources of activated fibroblasts [22, 25].

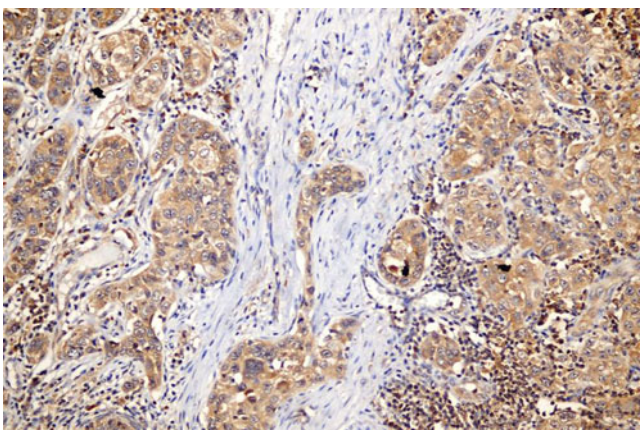

Fig. 4 Lack of expression of CD26 in the tumor stroma in SCC; strong positivity for this marker in the tumoral islands and in the lymphocytic infiltration (x20)

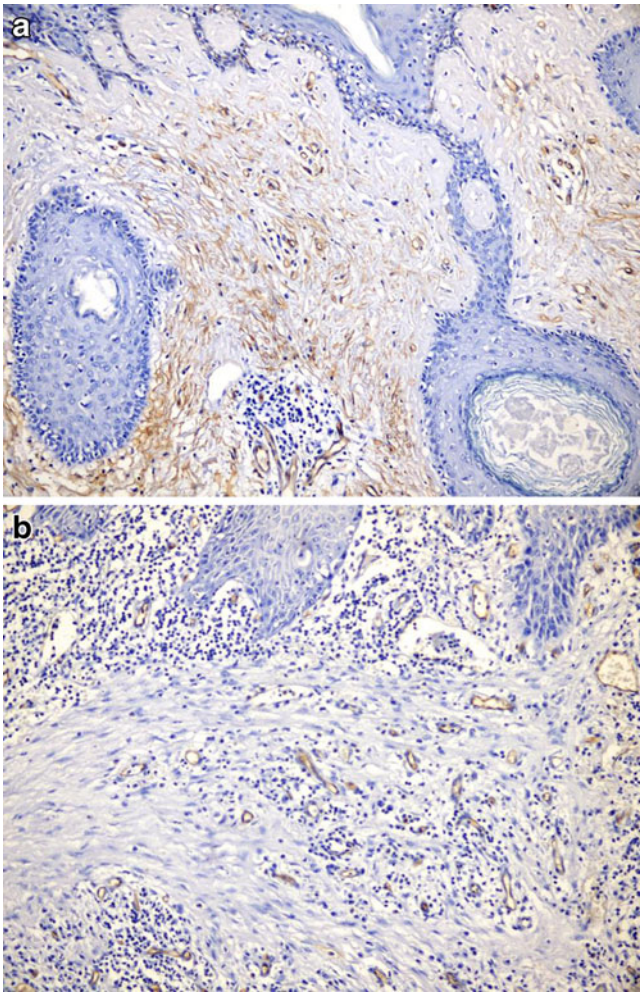

Fig. 5 **a**. Diffuse positivity (+++) for CD34 in the neighboring peritumoral stroma (SCC, x20). **b**. Loss of CD34 in the tumor stroma (SCC, x20)

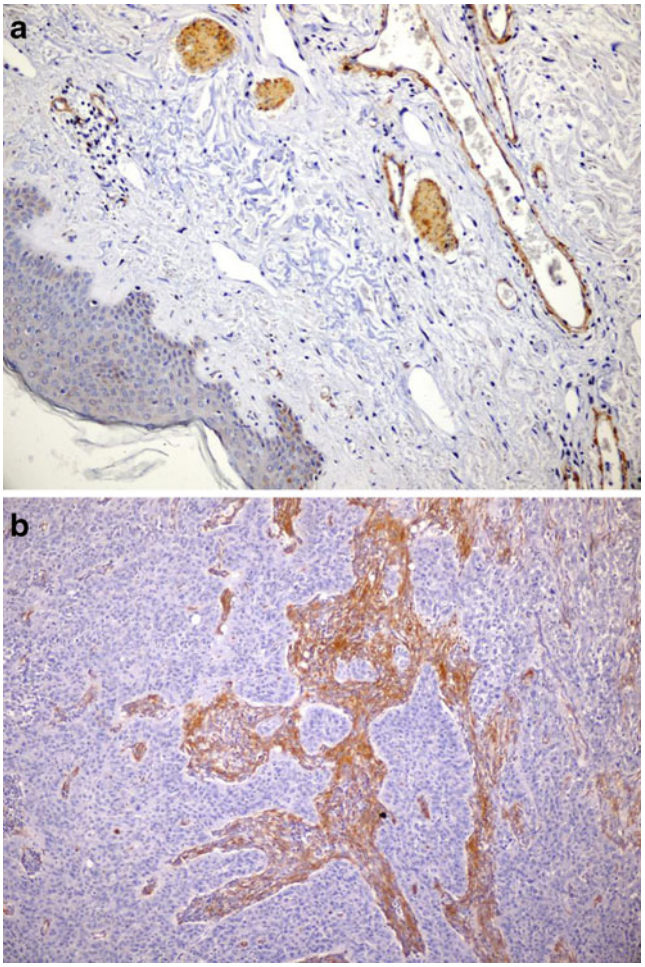

Fig. 6 **a**. Lack of actin expression in the neighboring stroma (SCC tumor margin, x 20). **b**. Strong myofibroblastic differentiation in tumor stroma (SCC, α-SMA x10)

The presence of CD34+ fibrocytes or dendritic interstitial cells in the stroma of normal tissues and neoplastic lesions and their relation to stromal myofibroblasts has also been studied in various sites. The CD34+ fibroblast in many organs is thought to represent an uncommitted cell capable of multidirectional mesenchymal differentiation, and it has been suggested that there is an inverse relation between CD34 expression and myofibroblastic differentiation [8].

Considering that CD34+ fibrocytes are antigen-presenting cells, their reduction or complete elimination enables an invasive tumor to escape immune-surveillance. This might constitute an important step in local tumor infiltration and distant tumor spread [4].

It has also been noted that the inverse relationship between CD34 and α-SMA in the tumor stroma might be related to the recruitment of circulating CD34+ cells derived from myeloid precursors and their conversion into myofibroblasts by tumor cells [4, 27].

CD26/DPPIV is a 110–120 kDa glycoprotein that hydrolyzes the carboxy-terminal side of dipeptide sequences.

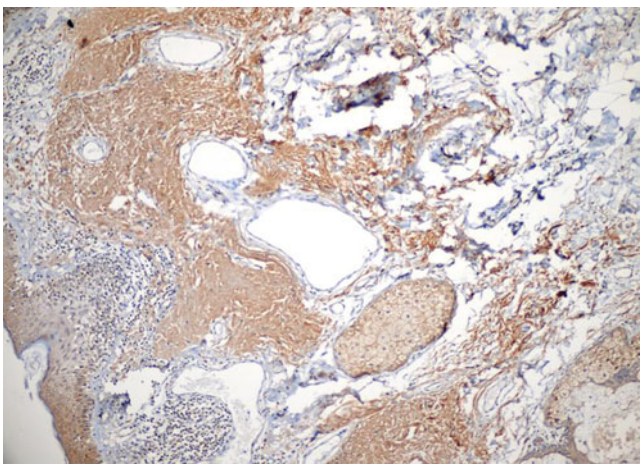

Fig. 7 Diffuse staining in collagen in the solar elastosis field in the neighboring stroma (SCC tumor margin, CD26, x10)

More recent studies focused mostly on the function of CD26 in extracellular matrix degradation [28] and angiogenesis, processes which lead to an increase in tumorigenicity and development of metastases [15, 16, 29]. It is noted that it may be involved in the cleavage of collagen, and in the inactivation of various cytokines [30]. Moreover, it is shown that CD26 not only binds to collagen [31, 32] but also to other matrix components such as fibronectin [33]. In addition, CD26 also acts as receptor for, and activator of, secreted proteinases [34]. CD26 inhibition is also claimed to promote antifibrotic effects [35, 36]. Inhibition of CD26 revealed alterations in collagen metabolism in rat experiments [37]. In one study, it was shown that inhibition of CD26 peptidase activity enhances homing, engraftment and competitive repopulation in congenic mouse bone marrow cell transplants [38]. It is also noted that CD26 may have an extra-enzymatic role in cell adhesion and migration on collagen and fibronectin [36]. Recent studies showed a linkage between CD26 and down-regulation of certain chemokines and mitogenic growth factor and degradation of denatured collagens (gelatin), suggesting that CD26 has a role in the invasive cell phenotype [39].

Review of the Data in the Present Study

In accordance with previous studies regarding other various anatomical sites, the present investigation demonstrates a phenotypical change in the stroma associated with invasive SCCs of the skin, consisting of a loss of CD34+ fibrocytes paralleled by a gain of α-SMA+ myofibroblasts. On the other hand, the stroma of peritumoral tissue, SK and non-tumoral skin samples contained CD34+ cells with no α-SMA+ myofibroblasts.

These results suggest that disappearance of CD34+ stromal cells and appearance of SMA+ stromal myofibroblasts are related. Similar results have been reported in the laryngeal SCC. Near-complete disappearance of CD34+ stromal cells in the tumor stroma led us to think that they might have been transformed into myofibroblasts. It has been suggested that scattered CD34+ cells throughout the body may represent the resident cells capable of multidirectional differentiation to myofibroblasts.

CD26 overexpression has been observed in several kinds of cancer tissue; however, there are few studies concerning the expression of CD26 in SCCs. Moreover, to date and to our knowledge, there are not yet any studies in skin SCC. In this study, we found that the peritumoral stromal CD26 staining was more prominent when compared to that of tumoral stroma. The most striking finding about CD26 was its strong positivity in solar elastosis fields in the peritumoral stroma. This finding led us to make the assumption that CD26 may play a role in the pathogenesis of this lesion.

Conclusions

To our knowledge, this is the first study in the literature to show the expression profiles of CD34, α-SMA and CD26/DPPIV in skin SCC, and the data are shown in a comprehensive way with many statistical analyses between control groups and tumoral and peritumoral tissue. According to the results of our study, it seems likely that in the process of cancer development, tumor cells influence underlying stromal cells to downregulate CD34 and acquire the expression of SMA in skin SCC, which is compatible with the other studies on the subject for different localizations. α-SMA and CD34 seem to be equally successful in distinguishing between benign and malignant lesions. In contrast with some of the previous findings in the literature (studied for localizations other than skin), expression patterns in peritumoral tissue (including solar keratosis) of these markers did not differ from benign lesions. We believe this finding should be verified in future studies comprising the preinvasive squamous lesions classified not only according to cytological atypia (i.e. solar keratosis and Bowen's disease), but which also take architectural dysplasia into account. We suggest that this finding should be used with precaution in routine work, because fibrotic scars may also show these phenotypical changes in the stroma. On the other hand, in this study, we have also shown that CD26 stromal expression was much more prominent in the neighboring stroma when compared to the tumor stroma. This finding can also be attributed to strong positivity of the collagen in the solar elastosis fields, which necessitates further work on the role of CD26 in collagen metabolism and in the pathogenesis of this lesion.

We hope that the present study leads to further studies on the different immunohistochemical behavior of intratumoral and extratumoral stroma in skin carcinoma and may help to understand better the steps of transition a benign epithelium into premalignant and malignant ones.

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