

Epithelial and Stromal Expression of Syndecan-1 (CD138) in Cutaneous Basal Cell Carcinoma

Vladimír BARTOŠ¹ and Milada KULLOVÁ²

¹Department of Pathology, Faculty Hospital in Žilina, V. Spanyola 43, Žilina, 012 07, Slovakia ²Department of Dermatovenerology, Faculty Hospital in Žilina, V. Spanyola 43, Žilina, 012 07, Slovakia

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ABSTRACT

Syndecan-1 (Sdc-1) is an important regulator of cell-cell and cell-extracellular matrix interactions. It is significantly involved in the carcinogenesis and tumor progression in many human malignancies. We immunohistochemically investigated Sdc-1 expression in cutaneous basal cell carcinoma (BCC) in order to clarify, whether there is difference in the expression pattern related to tumor growth characteristics. The study group consisted of 46 BCCs cathegorized into non-infiltrative and infiltrative growth variants. Specific antibody against Sdc-1 (clone MI15) was used for staining. There were 4 cases (8.7%) with preserved and 40 cases (87%) with reduced epithelial Sdc-1 expression, of which 20 cases were slightly and 20 cases severely reduced. Two BCCs (4.3%) showed a completely negative staining. Further, there were 13 BCCs (28.3%) with focal immunoreactivity in adjacent peritumorous stroma, all of which manifested infiltrative growth feature. We did not confirm a significant association between the expression of Sdc-1 in tumor tissue and both, noninfiltrative and infiltrative BCC variants. However, there was a significant association between the stromal immunoreactivity for Sdc-1 and infiltrative growth pattern of tumor. Sdc-1 expression was commonly reduced in neoplastic epithelial BCC tissue regardless of histologic subtypes. It did not clearly appear to be associated with tumor invasiveness. However, immunoreactivity in adjacent peritumorous stroma was found only in BCCs with infiltrative growth pattern, most of which showed apparent loss of Sdc-1 in epithelial cancer tissue. This immunostaining pattern could be a sign of more aggressive biologic behaviour of BCC.

Key words: Basal cell carcinoma, Biological behaviour, Syndecan-1 (CD138)

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| Corresponding author: Vladimír BARTOS | and participates in cellular proliferation, | | | |
| e-mail ⊠vladim.bartos@gmail.com | migration a histomorphogenesis [1]. | | | |
| Received: 02/04/2017 | Downregulation of syndecan-1 (Sdc-1) | | | |
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| | expression in epithelial cells results in loss of | | | |
| INTRODUCTION | cell polarity associated with a reduced level of E- | | | |
| | cadherin on the cell surface [1]. Of importance, it | | | |
| Syndecans are a group of transmembrane | is significantly involved in the tumor | | | |
| henaran sulfate proteoglycans known to | development and progression. However, it | | | |
| regulate multiple biological processes at the call | displays the Janus face" attittude because it | | | |
| regulate multiple biological processes at the cell | may be differentially synnaged in various | | | |
| surface and within the extracellular matrix. In | may be uniferentially expressed in various | | | |
| vertebrates, four syndecan genes (syndecan-1, - | cancers. While loss of Sdc-1 expression | | | |
| 2, -3, and -4) are present. Syndecan-1 (CD138), | correlates with the gain of cancerous | | | |
| the prototypical member of syndecans family is | characteristics in the majority of human | | | |
| prodominantly produced in onitholial colls | malignancies [2-8], in another tumors, its | | | |
| predominantiy produced in epitheniai cens, | increased expression also coincides with | | | |
| lymphoid cells in distinct stages of | increased expression also coincides with | | | |
| differentiation, and transiently also in | adverse outcomes [9-12]. In our previous work | | | |
| mesenchymal tissues [1]. This membrane-bound | [13], we have studied similar cell-cell adhesion | | | |
| protein functions as an important regulator of | epithelial molecule, E-cadherin in cutaneous | | | |
| cell_cell and cell_extracellular matrix | BCC tissue. In the current paper, we focused on | | | |
| interesting and con-excludential induity | immunohistochemical investigation of Sdc-1 | | | |
| interactions, acts as a growth factor coreceptor | minutonistochennear investigation of Suc-1 | | | |

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expression status in cutaneous BCC in order to clarify whether there is difference in the expression patterns related to tumor growth characteristics.

MATERIAL AND METHODS

Biopsy samples from 46 chosen cases of cutaneous BCCs from 41 patients were enrolled into the study. All specimes were histopathologically investigated at the Department of Pathology in Faculty Hospital in Zilina (Slovakia). We selected a set of representative samples of cutaneous BCCs of various histological subtypes, which were divided into two growth variants. The first one comprised 29 low-risk (non-infiltrative) BCC subtypes (superficial, nodular, superficialnodular). The second one included 18 high-risk BCCs subtypes with (at least focal) infiltrative pattern (nodular-infiltrative, growth infiltrative). Biopsy samples were routinely processed and immunohistochemical stained for Sdc-1 (CD138) according to manufacturer's instructions and finally evaluated in the light microscope. Specific monoclonal mouse antibody against Sdc-1 (clone MI15, DAKO, ready to use) was used for staining. Positive reaction on epidermis and eccrine glands served as internal control. The strong intensity of immunostaining in tumour cells was considered when it was as strong as in the normal epidermis. Since Sdc-1 is expressed in similar fashion and possess similar cell-cell adhesion function like E-cadherin, based on our previous paper [13] addressing E-cadherin expression in BCC, originally adopted from Pizzaro et al. [14], differed four cathegories of Sdc-1 we immunoreactivity: a) BCC with preserved expression (> 75% of the tumour cells were strongly stained), b) BCC with slightly reduced expression (> 25% of the tumour cells were positively stained but < 75% of the tumour cells were strongly stained), c) BCC with severely reduced expression (> 75% of tumor cells were not stained), and d) BCC with absent expression. For statistical analysis, they were merged into two separate subsets: a) preserved/slightly reduced and, b) severely reduced/absent. Immunoreactivity for Sdc-1 in peritumorous stroma was defined simply as positive or negative.

RESULTS

Sdc-1 showed mixed membranous and cytoplasmic staining in epithelial tumor cells,

usually of lower intensity compared with intact epidermis or eccrine glands. No nuclear immunoreactivity was detected. Overall, there were 4 cases (8.7%) with preserved (all superficial subtypes) (Figure 1) and 40 cases (87%) with reduced epithelial expression, of which 20 cases were slightly and 20 cases severely reduced (Figure 2 and 3). In addition. two BCCs (4.3%) (both infiltrative subtypes) showed a completely negative staining. When we statistically assessed two above-mentioned subsets of Sdc-1 expression in tumor tissue, i.e. preserved/slightly reduced vs. severelv reduced/absent. we have not confirmed a significant correlation between them and both, non-infiltrative and infiltrative BCC variants (p = 0.4). In spbite of that, there was a slight predominance of BCCs with infiltrative growth pattern in the subset of tumors having severely reduced or absent expression compared with non-infiltrative BCC variants (55.6% vs. 41.4%, respectively). Further, we confirmed 13 BCCs (28.3%) with focal weak to moderate immunoreactivity in surrounding peritumorous stroma, which was normally devoid of Sdc-1 production. Among them, five had slightly reduced, seven severely reduced, and single one had completely absent expression in the cancer these "stroma-positive" cells. All cases histomorphologically manifested infiltrative growth and stromal staining usually occurred at the invasive front of tumor nests (Figure 4). We observed a significant association between the stromal immunoreactivity for Sdc-1 and infiltrative growth pattern of tumor (p < 0.001). summary of the immunohistochemical Α findings in our set of BCCs investigated is presented in Table 1.

DISCUSSION

Deregulation of cell-cell adhesion molecule Sdc-1 often results in the development and progression of various malignancies, which arise from multiple pro-tumorigenic processes including increased cell proliferation and survival, motility, angiogenesis and extracellular matrix re-arrangement. Present paper describes immunohistochemical expression status of Sdc-1 in a set of 46 cutaneous BCCs. We have found that the vast majority of the cases (42; 91.3%) were accompanied by reduced epithelial expression, of which 22 cases were severely reduced or completely absent.

| BCC subgroup | Expression of Sdc-1 in tumor tissue | | Expression of Sdc-1 in peritumorous stroma | |
|------------------|-------------------------------------|------------|---|------------|
| non-infiltrative | preserved | 4 (13.8%) | no | 29 (100%) |
| (29 cases) | slightly reduced | 12 (41.4%) | present | 0 (0%) |
| | severely reduced | 12 (41.4%) | - | |
| | absent | 0 (0%) | | |
| infiltrative | preserved | 0 (0%) | no | 5 (27.8%) |
| (18 cases) | slightly reduced | 8 (44.4%) | present | 13 (72.2%) |
| | severely reduced | 8 (44.4%) | - | |
| | absent | 2 (11.2%) | | |

 Table 1. A summary of the immunohistochemical findings in the set of 46 BCCs we evaluated.



Figure 1. Preserved expression of Sdc-1 in superficial BCC. (original magnification 100x)



Figure 2. Severely reduced expression of Sdc-1 in superficial-nodular BCC. (original magnification 100x).



Figure 3. Severely reduced expression of Sdc-1 in nodular BCC. (original magnification 100x).

There is no doubt, downregulation of Sdc-1 gene significantly participate in BCC carcinogenesis. However, it is questionable, whether loss of Sdc-1 production in neoplastic cells parallels aggressive tumor growth. Reduced membranous

or cytoplasmic expression of Sdc-1 in epithelial tumor cells has been proven as adverse prognostic indicator in several human neoplasms, including stomach carcinoma [2], colorectal carcinoma [3], pulmonary squamous cell carcinoma [4], esophageal squamous cell carcinoma [5], extrahepatic bile duct adenocarcinoma [6], intrahepatic cholangiocarcinoma [7] or endometrial carcinoma [8]. However, even enhanced Sdc-1 expression in cancer cells has correlated with adverse clinical outcome in several neoplasms, for example breast carcinoma [9], pancreatic adenocarcinoma [10,11] or carcinoma of the thyroid gland [12]. Further, nuclear localization of Sdc-1 has been reported for some tumors [15,16], although biological impact of this rare phenomenon is not well understood. In addition, several studies have shown that peritumorous stromal expression of Sdc-1 was also associated with more aggressive tumor phenotype [2,8,10,12]. To the best of our knowledge, only two papers addressing immunohistochemical assessment of Sdc-1 in BCC of the skin have been published until now. In 2000, Bayer-Garner et al. [17] first investigated it in cutaneous BCCs of various histological subtypes. They found that with increasing tumor aggressiveness, Sdc-1 expression was lost from the surface of the neoplastic cells.



Figure 4. Virtually absent expression of Sdc-1 in infiltrative BCC with stromal positivity around the tumor nests. (original magnification 400x)

However, within the dermis, immunopositivity for Sdc-1 was present in areas adjacent to aggressive tumors. They concluded, this pattern of staining indicated that Sdc-1 was primarily produced by stromal cells rather than being shed by the carcinoma cells into the stroma. Ten years later, Kim et al. [18] investigated 10 nodular BCCs and 10 cases of high-risk BCC micronodular (infiltrative and histologic subtype). They found, while in nodular subtype, Sdc-1 was expressed as similar intensity to normal epidermis, in high-risk BCCs, it showed decreased staining intensity relative to that found in the normal skin. Both the abovementioned works have indicated that reduced expression of Sdc-1 in BCC was associated with the tumor aggressiveness and high-risk histologic subtypes, although the second one was very limited due to the small number of cases investigated. Our results are not in line with them in that we did not confirm a significant difference in tumor Sdc-1 expression between the non-aggressive and aggressive BCC variants. On the other hand, we have observed association between the infiltrative growth pattern of cancer and expression of Sdc-1 in peritumorous stromal cells. This corroborates findings of Bayer-Garner et al. [17] in cutaneous BCC, as well as other authors addressing another types of malignancies [2,8,10,12]. Probably a production of Sdc-1 in stromal fibroblasts promote a formation of abnormal extracellular matrix that may be more permissive to cancer cells migration and invasion. This finding needs to be better explained in the future. expecially as accumulating evidence suggest [19,20] that cutaneous BCC has a specific stroma requirement for its growth and tumor aggressiveness is greatly influenced by surrounding tissue microenvironment. Some authors [19] showed unique molecular phenotype of cancer-associated fibroblasts in BCC possibly accounting for diseae-specific histopathological roles including stromadependency. In the present study, "Sdc-1positive" peritumorous stroma was usually found around the "Sdc-1-severely reduced" cancer nests. It seems likely, these changes in Sdc-1 expression, i.e. induction in the stroma accompanied by reduction or loss in the malignant cells, could be critical in promoting the aggressive BCC phenotype. This area may represent a promising subject for further research.

In conclusion, our study demonstrated that expression of Sdc-1 was commonly reduced in neoplastic epithelial BCC tissue regardless of tumor histologic subtypes. It did not clearly appear to be associated with tumor invasiveness. However, immunoreactivity in adjacent peritumorous stroma was found only in BCCs with infiltrative growth pattern, most of which showed apparent loss of Sdc-1 in epithelial cancer tissue. This immunostaining pattern could be a sign of more aggressive biologic behaviour of BCC.

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Authors contribution

Vladimír BARTOŠ – concept for study design, data collection, statistical analysis Milada KULLOVÁ – literature review

Conflict of Interest

None declared.

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