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Review

Adhesion Molecules in Non-melanoma Skin Cancers: A Comprehensive Review

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Abstract. *Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most frequently diagnosed cancers, generating significant medical and financial problems. Cutaneous carcinogenesis is a very complex process characterized by genetic and molecular alterations, and mediated by various proteins and pathways. Cell adhesion molecules (CAMs) are transmembrane proteins responsible for cell-to-cell and cell-to-extracellular matrix adhesion, engaged in all steps of tumor progression. Based on their structures they are divided into five major groups: cadherins, integrins, selectins, immunoglobulins and the CD44 family. Cadherins, integrins and CD44 are the most studied in the context of non-melanoma skin cancers. The differences in expression of adhesion molecules may be related to the invasiveness of these tumors, through the loss of tissue integrity, neovascularization and alterations in intercellular signaling processes. In this article, each group of CAMs is briefly described and the present knowledge on their role in the development of non-melanoma skin cancers is summarized.*

Non-melanoma skin cancers (NMSC) are the most frequently diagnosed malignancies and their prevalence has increased dramatically over the last 30 years. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) represent 99% of all NMSC. BCC, which constitutes 70% of NMSC develops from basal epithelial cells of hair follicles or pluripotent epidermal basal cells and has a metastatic rate of only 0.0028-0.05% (1). Depending on the different features of tumor cells, there are many histological types of BCC, with different, but still low metastatic potential (2). SCC develops from the proliferating squamous layer of the epidermis, shows a metastatic rate of 0,1-9,9% and contributes to approximately 75% of deaths due to NMSC (3, 4). Although both skin cancers generally have a good prognosis, due to their high prevalence, they generate significant medical and financial problems worldwide. The most important risk factor of NMSC is exposure to the ultraviolet radiation, and both ultraviolet (UV) B and UVA play crucial roles in skin carcinogenesis affecting every stage, including direct cellular damage, production of reactive oxygen species, DNA alterations, and impairment of cell-mediated immune response (5).

A wide variety of risk factors of NMSC is known, such as Fitzpatrick I and II skin phototypes, age over 50 years, family history of skin cancers, chronic immunosuppression, long-lasting ulceration, and scars. In addition, exposure to carcinogenic substances, like arsenic and tobacco, HPV viruses, actinic keratosis, and chronic dermatoses, including lichen sclerosus, lupus erythematosus, and lichen planus, are associated with a higher risk of SCC (6).

Carcinogenesis is a very complex process; it is mediated by various proteins and pathways and characterized by genetic and molecular alterations. Changes in the expression or function of cell adhesion molecules (CAM) are involved in all steps of the progression of the malignancy, starting from the detachment of tumor cells from the primary site, intravasation into the blood, extravasation into distant tissues and formation of the secondary lesions.

Hence, the aim of the present review was to summarize the present knowledge on the role of CAM in the development of non-melanoma skin cancers.

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Cell Adhesion Molecules: Division, Functions, and Physiological Involvement

Cell adhesion molecules are transmembrane proteins responsible for cell-to-cell and cell-to extracellular matrix adhesion (7) playing also a crucial role in intercellular signaling and the structure of the extracellular microenvironment. Moreover, they play important roles in physiologic processes like embryogenesis and organ growth, cell migration and differentiation, and wound healing, and are fundamental elements for the maintenance of tissue integrity. However, over 100 different CAM participate in a variety of pathological processes such as inflammation, tumor invasion and metastasis (7). Changes in the expression and function of CAMs have been recently extensively studied. Based on their structures they are divided into five major groups: cadherins, integrins, selectins, immunoglobulins and CD44 family (Table I).

Cadherins

Cadherins are transmembrane glycoproteins and the most studied group of adhesion molecules, divided into classic cadherins (including E-epithelial, N-neural, P-placental), which are the main mediators of calcium-dependent cell-cell adhesions, and nonclassic cadherins, including desmosomal cadherins and newly discovered protocadherins (8). These adhesion molecules play a pivotal role during embryogenesis and morphogenesis and also in the maintenance of adult tissue architecture (8). They are widely present in the normal epithelium and determine its integrity. Major cadherins in the skin include E-cadherin and the desmosomal cadherin desmoglein 1 (9).

E-cadherin mediates interactions between keratinocytes and also between keratinocytes and Langerhans cells, which are the main immune cells of the skin (10, 11). Classic cadherins are composed of five extracellular domains, a transmembrane segment and an intracellular domain. The most studied and first identified is E-cadherin, also known as cadherin-1 or epithelial cadherin, which is expressed in almost all epithelial tissues and is responsible for epithelial integrity and cell polarity (12). The cytoplasmic domain of E-cadherin interacts with groups of cytoplasmic regulatory proteins called catenins, which mediate binding of the complex to cytoskeletal actin filaments. The E-cadherin–catenin complex plays a key role in cellular adhesion, regulates cadherin stability, and functions in cell signaling (13). In the normal skin, E-cadherin shows homogeneous membranous distribution in the whole epidermis, with the exception of the lower pole of basal keratinocytes, which are in contact with the basement membrane (10).

Loss of expression or impairment of the function of E-cadherin leads to loss of cell polarity and changes in tissue architecture. The epithelial cells may acquire a mesenchymal-like phenotype, detach from their neighboring cells and migrate, and in case of neoplasms form metastases. This process is called epithelial-mesenchymal transition (EMT) and the loss of E-cadherin and expression of N-cadherin, often called the “cadherin switch”, is considered as the most important indicator of this phenomenon (1). In this context, E-cadherin is also known as a metastasis suppressor protein (14, 15).

Several studies showed abnormal expression of E-cadherin in various skin carcinomas. In BCC, there is an overall tendency for lower expression of E-cadherin, when compared with normal skin, and low expression is more frequently observed in the more aggressive histological types of the tumor (16-19). The observed reduction of E-cadherin expression was more pronounced in the infiltrative and morpheaphorm BCCs, while the superficial and nodular types generally demonstrate less reduced expression of this molecule (17, 20). Moreover, with the higher invasiveness of the tumor, the membranous expression of E-cadherin is reduced and the cytoplasmic expression is increased (21). It is consistent with the current state of knowledge that high E-cadherin expression in the cell cytoplasm and low expression in the cell membrane may be associated with tumor aggressiveness. In support, it has been suggested that correct cell adhesion requires strong membranous activity of E-cadherin (22, 23).

In contrast, it is noteworthy that there are reports revealing no difference in the expression of E-cadherin in the BCC specimens, regardless of their histological type (24-26). A possible explanation of such discrepancy could be the different tissue fixation methods used (25).

The results of the studies in SCC are more consistent. In almost all analyzed SCC specimens, the expression of E-cadherin was reduced compared with normal epidermis (18, 23-24, 27-32) and this reduction was more pronounced in less differentiated and more invasive tumors (29, 33). However, the contribution of lower levels of E-cadherin in the metastatic process is still debatable, with conflicting results demonstrating either lower or a similar expression of this molecule in tumors with and without lymph node metastases (24, 25), although once more, the different fixation method utilized in one of those studies could explain such difference (25).

Many studies on E-cadherin showed its contribution in both SCC and BCC, but only a few investigations have been conducted on N-cadherin in NMSC. N-cadherin is not found in normal squamous epithelium, although is known for angiogenesis stimulation in some cancers (33). In BCC, N-cadherin was found to be up-regulated in the metastatic, but not in non-metastatic tumors (34), while in SCC, the tumors expressing N-cadherin demonstrated higher invasiveness (35). The low number of publications concerning N-cadherin

Table I. *The major families of cell adhesion molecules involved in the pathogenesis of non-melanoma skin cancers.*

Family	Members with importance in the skin	Involvement in pathogenesis of non-melanoma skin cancers
Cadherins (more than 100 different types)	Classic: -E -N -P Desmosomal: -Desmocollins -Desmogleins Unconventional: -T	Epithelial-mesenchymal transition Cell adhesiveness Markers of epithelial differentiation
Integrins Heterodimers of subunits α and β	-α2β1 (collagen receptor) -α3β1 and α6β4 (laminin receptors) -α5β1(fibronectin receptor)	Single cell migration Metastases Signaling
Selectins	E	Metastases
Immunoglubulin family (IgSF)	ICAM, VCAM, PECAM, NCAM Nectin family	Marker of neovascularization
CD44*	CD44s, CD44v6-9	Marker of intercellular matrix instability

*The CD44 family consists of the standard CD44s and at least 10 CD44v isoforms.

in NMSC might indicate that the EMT phenomenon in which cells lose epithelial and acquire mesenchymal markers needs further investigations in both SCC and BCC, as its mechanism might involve additional molecules, not yet assessed in these tumors.

Like other classic cadherins, P-cadherin is important for cell differentiation during embryonic development as well as for the maintenance of normal architecture of mature tissues (12). This molecule is present in the cells of the basal layer of the normal epidermis, therefore is considered as an indicator of proliferation, and is usually co-expressed with E-cadherin (36, 37). However, both BCC and especially the peripheral sites of non-metastatic SCC specimens, demonstrate P-cadherin expression similar to the normal skin, whereas lower expression is observed only in the metastatic SCCs (36, 38). Hence, it appears that it does not play a significant role in skin carcinogenesis.

Nonclassic cadherins - desmogleins (DSG) and desmocollins (DSC) - play the role in the formation of desmosomes, which are the structures connecting epithelial cells. Desmoglein 1 is localized mainly in the superficial upper layers, and desmoglein 2 and 3 in basal and suprabasal layers of the normal epidermis, respectively (39). Desmocollins and desmogleins are localized in the upper layer 2 and 3 in the lower layers of the epithelium, respectively (39).

Expression of DSG1 was found to be significantly reduced in all cases of SCC and in cases of nodular BCC, and completely absent in the morpheaphorm and superficial types of BCC (40). Similarly, the reduced expression of DSG3 has also been demonstrated in BCC specimens (39). In contrast, DSG2 is significantly more intensively expressed in both types of NMSC, and its higher expression occurs more frequently in poorly differentiated SCCs (39, 41). The discordant expression of these molecules might be related to the fact that DGS2 is regarded as a protein associated with proliferation and aggressiveness of tumor cells, and a marker of lower differentiation (42). As only insignificant differences in the expression of DSC 1-3 in the NMSC have been reported so far, their role in cutaneous carcinogenesis is still not unequivocal (43).

T-cadherin belongs to the nonclassical cadherins and in normal skin is expressed on keratinocytes of the basal cell layer of the epidermis. Although its function in the biology of the skin remains unclear, it has been considered as a suppressor of tumourigenesis in various cancers (9, 44). Although low expression of T-cadherin has been observed in both BCC and SCC (44-46), there is contradictory evidence of even higher expression in BCC specimens, regardless of the histological type (47). Therefore, the role of this adhesion molecule in the development of NMSC appears to be much more complicated and requires further investigations (46, 48).

Integrins

Integrins are heterodimeric transmembrane proteins composed of α and β subunits. At present, 18 α and 8 β subunits have been discovered, which in several combinations form 24 integrin complexes (49). These

adhesion molecules consist of a larger extracellular domain, a single transmembrane domain, and a relatively small intracellular domain. The extracellular domain binds with connective tissue components such as collagen, fibronectin, laminin, whereas the intracellular domain of integrins interacts with the cytoskeleton. The integrins participate in cell-matrix and also in cell-cell adhesion and play an important role in various physiological processes including embryological development, hemostasis, wound healing, and signal transduction (7, 50).

The main integrins of normal human epidermis are α2β1 (collagen receptor), α3β1 and α6 β4 (mainly laminin receptors). The α5β1 and αvβ6 integrins (receptor for fibronectin) are expressed at nearly undetectable level in normal epidermis and their expression increases significantly during wound healing (51, 52). Integrins are known to be involved also in EMT. The "cadherin switch" discussed in the previous paragraphs of this article, is also characterized by changes in the expression of integrins from those containing β4 subunits, present in hemidesmosomes, to those containing β1 and β3 subunits, which results in a higher cellular motility (7, 53, 54).

Few studies on the expression of integrins in NMSC have been conducted. Studies on the expression of α2 β1 and α3 β1 integrins in BCC specimens have revealed high levels of these two adhesion molecules, with a tendency for a higher expression in nodular type compared to the morpheaform (52, 55-57). Moreover, localization of α3β1integrins corresponded to areas with preserved basement membrane (52). Furthermore, epithelial cells of BCC expressed also αv, α4 and α5, which were not present in the normal epidermis (58).

Staining of SCC for α2β1, and α3β1 subunits showed absence or low expression of these integrins, which could be related to higher malignancy of SCC compared with BCC (52).

Selectins

Selectins (Lec-CAM) are calcium-dependent transmembrane proteins composed of an N-terminal lectin domain, an epidermal growth factor (EGF) domain, 2-9 protein repeats, a transmembrane domain and a small cytoplasmic domain (59). This class of adhesion molecules consists of endothelial (E), leukocyte (L) and platelet (P).

E-selectin in normal skin demonstrates a weak expression in the microvessels and - so far - it seems to be the only selectin involved in cancer metastatic activity, probably through the interactions between endothelial cells and tumour surface selectin ligands (50, 60). The results of studies on the expression of E-selectin in the normal skin and NMSC revealed its negative expression in normal skin and positive expression in SCC and BCC. Moreover, in cases of SCC, there was a strong positive staining for E-selectin on malignant keratinocytes and vascular endothelium. In contrast, no tumour cell staining, but endothelial expression of E-selectin was observed in BCC (61). Hence, future studies are warranted to examine the involvement of selectins in the biology of NMSC (62, 63).

CD44

The transmembrane cell surface molecule CD44, which is present multiple isoforms, is broadly distributed in a wide variety of tissues, including the skin, where it is distributed in the hair follicles, sweat glands and in the epidermis with the exception of the basement membrane and granular and corneous layers (64). The physiological distribution of CD44 is concordant with the distribution of hyaluronic acid as CD44 is thought to be a receptor for hyaluronic acid, and also an important ligand of E-selectin (50, 64, 65).

The presence of CD44 in NMSC is controversial, although, in BCC, there is an overall tendency for lower expression (66-71). Some inconsistency in the results of the published studies remains regarding SCC. Although some of them demonstrated that the expression of CD44 in SCC is reduced, and decreased CD44 expression is mostly found in the more invasive and aggressive tumors (65-66, 69, 72), other analyses did not confirm such findings (68, 71, 73). However, in one of the contradictory studies, the process of specimen preservation was substantially different, as the samples were frozen and not paraffin-embedded, hence the availability of the antigens was significantly higher (74).

The Immunoglobulin Family of Adhesion Molecules

Immunoglobulin-like cell adhesion molecules constitute the largest and most diverse group of adhesion molecules, which includes vascular cell adhesion molecules (VCAMs), intercellular adhesion molecules (ICAMs), neural cell adhesion molecule (NCAMs), platelet endothelial cell adhesion molecule (PECAM), and nectins (7, 49). All members of this family consist of an extracellular domain (which contains one or more immunoglobulin-like domains), a single transmembrane domain, and a cytoplasmic tail (75). The VCAM (CD106) is widely distributed and highly expressed primarily in the endothelial cells (76). Its expression increases, especially in states of inflammation, on tissue macrophages, dendritic cells and epithelial cells (76, 77). Moreover, it plays the role of an endothelial ligand for VLA-4 (Very Late Antigen-4 or integrin α4β1) of the β1 subfamily of integrins (78). A study on the expression of VCAM in SCC demonstrated its intense presence in poorly differentiated SCC, but only moderate expression in well-differentiated SCC (79). VCAM-1 was not detected in BCC tissues and negative or weak staining was observed in the epidermis adjacent to BCC (61, 80). The few publications concerning VCAM in NMSC might indicate that this

molecule does not play any significant role in skin cancer development, although its increased expression in SCC tumors could potentially support the role of inflammation in the pathogenesis of these neoplasms.

The ICAM family consists of five members (ICAM-1 to ICAM-5), which are important elements of intercellular, but not cell-matrix adhesion (81). ICAM-1 (CD54) contains five Ig-like domains and is only occasionally detectable on keratinocytes of the normal skin, mostly in the T-cell-present regions. It is, however, found on endothelial cells, since ICAM-1 is one of the most expressed endothelial surface adhesion molecules (78). The primary role of ICAM-1 in the human skin is adhesion to the LFA-1, present on circulatory leukocytes. Studies on ICAM expression on NMSC revealed lack of expression on BCC tumour cells (61, 80, 82-84) with minimal expression in the peritumoral stroma (80, 82, 84). In SCC, a dramatic increase in ICAMs in poorly differentiated SCC was shown, while in well-differentiated tumors, there was only focal ICAM expression (79). These results are consistent with the pathophysiology of NMSC, as ICAM-1 expression on keratinocytes increases in chronic inflammatory conditions, which contributes to the development of SCC, but not BCC (81).

NCAM (CD56), another member of the immunoglobulin family, has originally been found on neuronal cells. It plays an important role in morphogenesis, in neural development and mediates intercellular adhesion in various tissues (85). Studies on this adhesion molecule in BCC and SCC revealed strong immunoreactivity in the majority of stained BCC specimens regardless of their histological type, and negative expression in almost all SCC samples (86-89). These results could indicate the difference in the origin of these NMSCs. As the cells of the hair follicle in the normal skin also demonstrate positive immunoreactivity for NCAM, its strong expression in BCC could be a consequence of its development from these cells, which has been supported by studies in recent preclinical models (86, 90-91). However, other theories regarding the origin of BCC should also be taken into consideration (92, 93).

PECAM (CD31) is physiologically involved in leukocyte migration, signal transduction and angiogenesis (94, 95). Staining of NMSC for CD31 showed its elevated expression in the areas adjacent to both SCC and BCC, when compared with normal skin, with expression significantly higher in the areas surrounding SCC (80, 96). In the tumor area, CD31 was identified in SCC, but not in BCC (96). However, in another study, the expression of CD31 did not differ significantly between SCC and BCC cases, and no difference was observed when consecutive different grades of SCC progression or the presence of tumor metastases were analyzed (97, 98). Hence, it appears that the difference in the metastatic potential of squamous and basal cell carcinomas is not only due to differences in angiogenesis, but also in multiple other factors.

Nectin family comprises four members and regulates various cellular functions, such as mobility, adhesion, proliferation, polarization, and differentiation (99). In the normal skin, nectin 1α was colocalized with E-cadherin in cell–cell adherens junctions of the epidermis and was detected in all living layers of the epidermis with the strongest staining in the spinous layer (100). A study on the expression of nectin 1α in NMSC revealed a reduction in staining, more pronounced in morpheaphorm BCC and in SCC than in the solid type BCC, which is rather consistent with the expression of E-cadherin in NMSC. These results might potentially indicate that reduction of nectin expression could be associated with invasiveness of the tumor, but definitely require further investigation (100).

EpCAM (epithelial cell adhesion molecule) is considered a molecule involved in cellular signaling rather than a cell adhesion molecule, because structurally it does not resemble any of the five major families of CAM, and its classification as an adhesion molecule is still debatable. However, evidence derived from studies on various malignancies indicates that it might be also involved in the development of those pathologies (101).

Physiologically, EpCAM is expressed mainly in glandular epithelial cells, while in pathological conditions, it is mostly overexpressed on the cells of epithelial tumours, but not in non-epithelial tumors (101). There have been reports demonstrating positive staining for EpCAM across all types of BCC (102-105), while loss of its expression was identified in the front of the tumour and in its infiltrative islands (106). There was a negative expression of EpCAM in SCC, irrespective of the histological type or grade of differentiation (104, 105). Hence, although in non-cutaneous epithelial malignancies, increased expression of EpCAM has been considered as a predictor of worse clinical outcomes (107, 108), the evidence derived from studies on NMSCs appears to be insufficient to confirm such hypotheses.

Conclusion

Progression of cancer is a result of altered intercellular interactions and loss of adhesion between the neoplastic cells and the extracellular microenvironment. Numerous studies indicate that differences in the expression of adhesion molecules are related to the invasiveness of skin cancers. Downregulation of some, physiologically present, adhesion molecules has been recently suggested to be a sign of a higher tumor metastatic potential. While in the early stages, both SCC and BCC are treatable, in some cases especially SCC recurs locally and even metastasizes leading to death. Therefore, it is important to identify the more aggressive tumors that require closer follow-up. Besides established prognostic factors like size, anatomic site, clinical and histological type of a primary tumor, adhesion molecules

may become additional prognostic biomarkers of non-melanoma skin cancers. Cell adhesion molecules could be also an attractive therapeutic target because their extracellular domains could be easily accessed by antibodies or small-molecule inhibitors. Therefore, future research can open new perspectives for more effective skin cancer treatment.

Conflicts of Interest

The Authors declare that there are no conflicts of interest regarding the publication of this article.

Authors' Contributions

JCS and JPD contributed to study design, collection of data, writing of the manuscript's draft and the preparation of the final version of the article.

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