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2

Desmosomal Cadherins in Basal Cell Carcinomas

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1. Introduction

During recent years desmosomal research has developed into a biomedical field focused on the role of desmosomal components in tissue development and homeostasis. Investigators' area of interest involves the influence of cell adhesion defects and abnormal cell signaling on cancer invasion and metastasis. Some data indicated that there is greater cell proliferation activity in basal cell carcinoma (BCC) than suggested by the clinically apparent slow growth of the tumor. Indeed, it may suggest that individual desmosomal cadherins play different roles in proliferation and differentiation in BCC. Thus, the functional importance of desmosomal cadherins in the adhesion of carcinoma cells and during destructive/invasive growth makes them a useful tool for the evaluation of the biological behaviour of BCC.

2. Basal cell carcinoma: Clinical and histological subtypes

BCC is the most common type of skin cancer with rising incidence trends. It originates from basal cell layers of epidermis and/or the pilosebaceous adnexa (Yu et al., 2008). It is usually slow growing and rarely metastasizes; however, it can cause clinically significant local destruction and disfigurement when neglected or inadequately treated (Wong et al., 2003, Telfer et al., 2008). Prognosis is excellent with proper therapy. Growth of BCC is usually localized to the area of its origin (Bath-Hextall et al., 2004). BCCs typically occur in adults, but the tumors can develop even in children (Kossard et al., 2006; Hakverdi et al., 2011). Furthermore, males show higher incidence of BCC than females (Bath-Hextall et al., 2004). The etiology of BCC is still unclear but appears to be of multifactorial origin, resulting from a complex interaction of both environmental and genetic factors (Hakverdi et al., 2011).
Still, little is known about the genetic mechanisms underlying BCC (Teh et al., 2005). The genetic predisposition can be associated with, for example, genomewide allelic changes such as losses of chromosomal fragments leading to losses of heterozygosity (LOH) from a single DNA sample (Greinert, 2009), which are the most frequent genetic alternation in BCC (Gailani et al., 1996). In BCCs LOH is usually restricted to chromosome arm 9q (Greinert, 2009) and *de novo* mutations in the Patched 1 (*PTCH*) were found in 69% BCCs with 9q LOH (Teh et al., 2005). It was suggested that mutations in gene on chromosome 9q22 may be a necessary event for basal cell carcinogenesis (Gailani et al., 1996). Genes of importance to BCC development

include *PTCH1*, *P53* and *MC1R*, and many other recently discovered genes, which probably also play a role in BCC pathogenesis (de Zwaan & Haass, 2010). Moreover, twin studies and other studies of familial aggregation suggest a genetic predisposition to this cancer (de Zwaan & Haass, 2010). BCC may be divided into various clinical and histological subtypes. Using cDNA microarrays it is suggested that phenotypic diversity of BCCs might be accompanied by a corresponding diversity in gene expression patterns (Yu et al., 2008).
Various types of cutaneous lesions may be a clinical manifestation of BCC. There have been also many histological subtypes of BCC described by various authors. The highest number, 26 subtypes was described by Wade et al. (Wade & Ackerman, 1978). Thus, the nosology system of BCC requires simplification and clustering which may lead to a more practical classification (Mosterd et al., 2009). Clinical and histological subtypes of BCC may exhibit different patterns of behaviour and may even have a different etiology (Yu et al., 2008). The distinction between different BCC variants is important for prognosis and treatment (Yu et al., 2008).
There are two basic criteria in histological classifications of BCC: the histological growth pattern and histological differentiation. The growth pattern of BCC is probably associated with its risk for recurrence (Vantuchová & Čuřík, 2006).
According to WHO classification 2006 (Kossard et al., 2006) BCC may be divided into eight subtypes (Table 1):

	Clinical subtypes	**Histological subtypes**
Superficial	Characterized by a flat, red, well-circumscribed plaque with slow centrifugal spread. It may present as multiple lesions. Different sizes: from a few millimeters to over 10 cm in diameter. A fine pearly border or central superficial erosions with a history of contact bleeding may be present. It develops most frequently in areas where skin is covered (especially on the trunk). 10-30% of BCC	Presence of superficial lobules of basaloid cells which project from the epidermis or from the sides of follicles or eccrine ducts into the dermis and are surrounded by loose myxoid stroma. Usually there appear to be multiple tumor foci, separated by areas of normal skin.
Nodular	Elevated pearly nodules associated with teleangiectasia. It may become ulcerated or cystic. It develops most frequently on the head. 60-80% of BCC.	Presence of large lobules of basaloid cells ("germinative cells") with peripheral palisading of the nuclei. The lobules may have associated mucinous degeneration with cysts or have an adenoid pattern.
Micronodular	Elevated or flat infiltrative tumor. It develops most frequently on the back.	Presence of small nodules that permeate the dermis. In contrast to nodular BCC the surgical margins of micronodular BCC may be underestimated.
Infiltrating	Pale, indurated, poorly-defined plaque. It is most often found on the upper trunk or face.	Presence of strands, cords and columns of basaloid cells with scant cytoplasm.
Fibroepithelial	Elevated flesh coloured or erythematous nodule that may resemble a seborrhoic keratosis or acrochordon. It develops most frequently on the back.	Presence of an arborising network of cords of basaloid cells that extend downwards from the epidermis and create a fenestrating pattern.
With adnexal differentiation	No distinguishing clinical features.	Presence of adnexal differentiation including basaloid buds, ductal, sebaceous, and trichilemmal elements.
Basosquamous	No distinguishing clinical features.	Presence of abundant cytoplasm with more marked keratinization than typical BCC. The nuclei have vesicular chromatin with pleomorphism.
Keratotic	It appears pearly and may be studded with small keratin cyst (milia).	It shares the overall features of a nodular BCC. Keratinization may be laminated.

Table 1. Subtypes of BCC

Still, it should be emphasized that individual BCCs, when their total mass is examined, may exhibit combined features of various histological subtypes.

3. Desmosomal cadherins: Molecular biology and distribution in physiological and pathological conditions

Desmosomal cadherins (DCs) are transmembrane glycoproteins, which belong to the group of calcium-dependent intercellular adhesion molecules. They may initiate and maintain cell-cell adhesion in the absence of any contribution from classical cadherins (Garrod et al., 2002). DCs involve two subfamilies: i) the desmogleins (DSGs), ii) the desmocollins (DSCs) (Bazzi et al., 2006; Ishii, 2007; Brennan et al., 2004, Koch et al., 1992). So far three isoforms, each in two splicing variants, of desmocollin (DSC1-3) and four isoforms of desmoglein (DSG1-4) are known in humans (Ishii, 2007; Brennan et al., 2004). An additional two DSGs, DSG5 and DSG6, are present in mice (Whittock, 2003). Alternative splicing of the cytoplasmic domain gives rise to a longer "a" and a shorter "b" form of each DSC isoforms (Garrod et al., 2002). It is known that DSG and DSC have approximately 30% amino acid identity with each other and with the classical cadherins. They all have homologic basic structure in their extracellular domains and possess in the amino-terminal EC1 ectodomain cell adhesion recognition (CAR) sites with a central alanine residue. In light of above, researchers, using transfected fibroblasts, shown that adhesion mediated by DSC2/DSG2 and DSC3/DSG3 could be specifically blocked by peptides (Garrod et al., 2002).

In humans the genes encoding DCs are clustered on the q arm of chromosome 18 (Fig.1), so the possibility exists that DC gene expression is controlled through a common locus control element (Smith et al., 2004). Each DCs arise from a distinct gene and they are generally expressed in a differentiation-specific manner. This may suggest that in addition to their adhesive function, they may have a direct or indirect role in regulating differentiation (Garrod et al., 2002). Thus, the correlation between DCs and the stage of differentiation/proliferation allows creating the hypothesis that changes in gene function resulting from mutations would lead to alternation in differentiation/proliferation of hair follicle and epidermal cells (Cserhalmi-Friedman et al., 2001; Smith et al., 2004). This idea is supported by the results of transgenic mice experiment in which mis-expression or target ablation of DCs has resulted in altered patterns of epidermal differentiation. The DSGs genes are arranged in the following order: DSG1, DSG4, DSG3, DSG2 from centromeric to telomeric direction in the cadherin gene locus (Mahoney et al., 2006). Interestingly, this organization of genes correlates with DSGs expression in the epidermis (Mahoney et al., 2006). Thus, DSG1 and DSG4 are expressed in the differentiated cells of epidermis while DSG3 and DSG2 are localized to the proliferative basal and suprabasal cells of epidermis (Mahoney et al., 2006).

Various studies on adult human and bovine tissues have established that the DSGs and DSCs are both expressed in tissue-specific and differentiation-dependent patterns (King et al., 1993, 1997). This type of DCs expression implies that desmosomes within different tissues are biochemically, and presumably functionally, distinct (Delava et al., 2011). Delava et al. demonstrated that the precise role for the tissue-specific expression patterns of desmosomal cadherins is not fully understood, but manipulation of their expression suggests that this regulation is critical to tissue homeostasis (Delava et al., 2011).

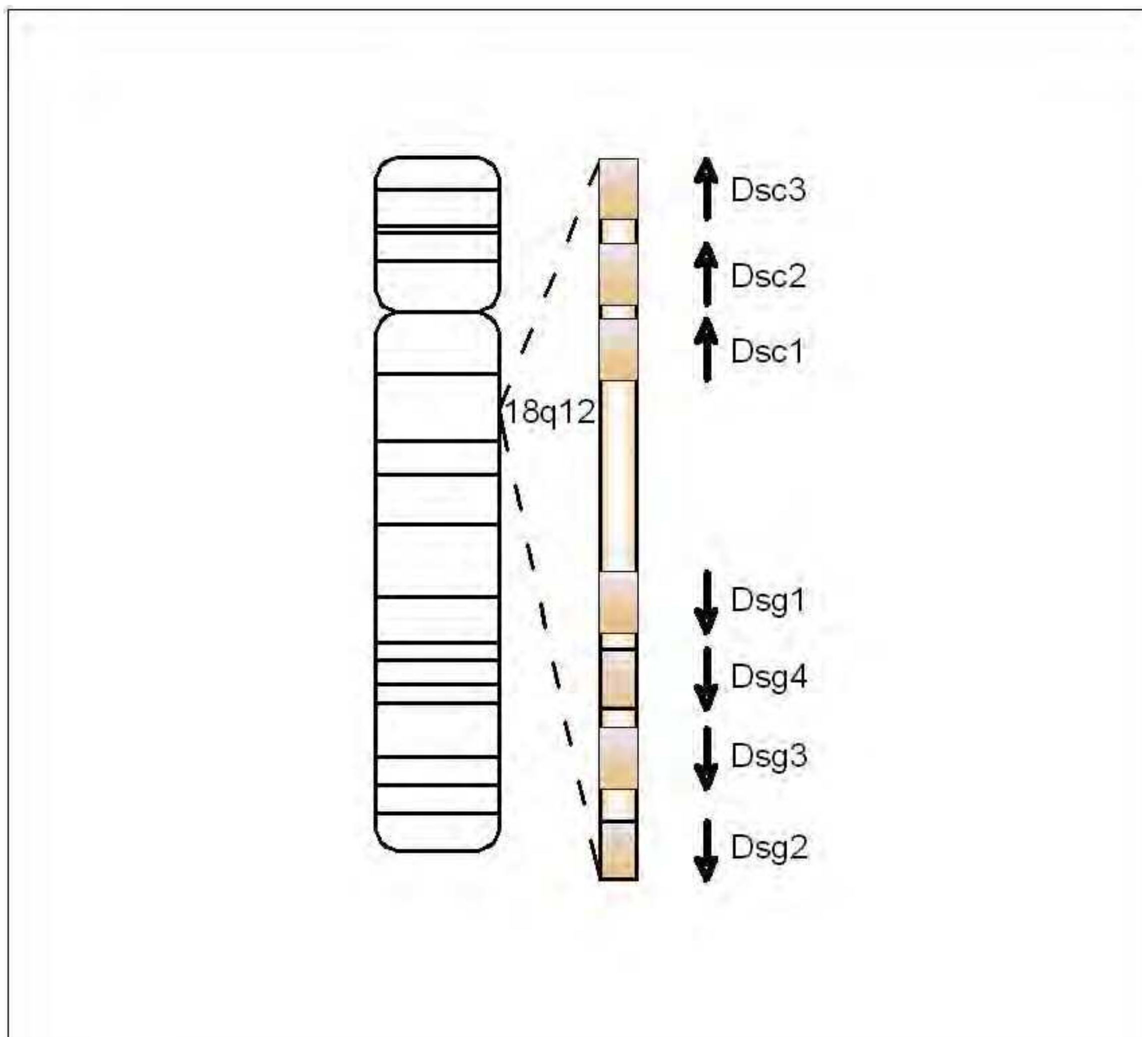

Fig. 1. Molecular biology of human desmosomal cadherins: genes reside in a genomic cluster on the q arm of human chromosome 18

3.1 Expression of desmosomal cadherins in normal tissue

The DCs show complex patterns of expression, particularly in intermediate layers where the majority of isoforms are expressed. However, the molecular mechanisms regulating DCs expressions are not well studied, particularly at the transcriptional level (Bazzi et al., 2006). Researchers, analyzing mRNA expression, suggested spatial patterns of DCs genes transcription and hierarchical expression of individual genes (King et al., 1997). However, most of the findings described the DC expression pattern at protein level. Nevertheless, Mahoney et al. (Mahoney et al., 2002) noticed that DSGs share high homology at both the gene and protein level and their expression is spatially and temporally regulated (existence of systems that provide both temporal and spatial control for transgene expression). This fact may potentially be contributing to significant role of DSGs in cell-cell adhesion during development (Mahoney et al., 2002). All desmosomes possess at least one DSC and one DSG but it appears to be no barrier to the presence of more than one of each (Chidgey, 2002; North et al., 1996; King et al., 1997). Data obtained with the use of mRNA and protein analyses shown that DCs are formed in the skin in relation to differentiation (Moll et al., 1997).

Expression pattern of DSGs in normal human epidermis was shown in Fig. 2. DSG1 and DSG3 are restricted to stratified epithelia (Brennan et al., 2010). DSG1 is more intensively expressed as the cells differentiate toward the stratum corneum, and very little detectable in the basal layer, whereas DSG3 is localized to the basal and immediate suprabasal layers (Wu et al., 2003). In normal human epidermis, DSG2 is expressed at low levels, and was reported to be restricted to the lowermost epidermis (Brennan et al., 2010). DSG2 expression fades with keratinocyte differentiation, whereas DSG3 expression decreases somewhat gradually from the basal into the spinous cell layers (Bowszyc-Dmochowska et al., 2010). DSG4 expression is restricted to the highly differentiated upper cell layers (Ishii, 2007), what is confirmed at both the mRNA and protein level (Bazzi et al., 2006). Expression of DSG4 may first be detected in the lower granular layers, increases in intensity upward into the horny layers, and terminates as the cells die to form the protective barrier (Mahoney et al., 2006). There is a hypothesis that DSG4 may coincide with the downregulation of DSG1 (Mahoney et al., 2006). Interestingly, the genes for DSCs are also differentially expressed. DSC1 is confined to the suprabasal cell layers, whereas DSC2 and 3 are found in desmosomes throughout the interfollicular epidermis (Moll et al., 1997).
Molecular cloning of DSGs and analysis of intron/exon organization of the DSG mice genes revealed significant conservation (Mahoney et al., 2002). Some studies indicated that expression of DSGs mRNA during mouse embryonic development and in various adult tissues are variable (Mahoney et al., 2002). This group of researchers shown that in adult mouse tissues, DSG2 is widely expressed while DSG1 and DSG3 expression is restricted to selected tissues (Mahoney et al., 2002).

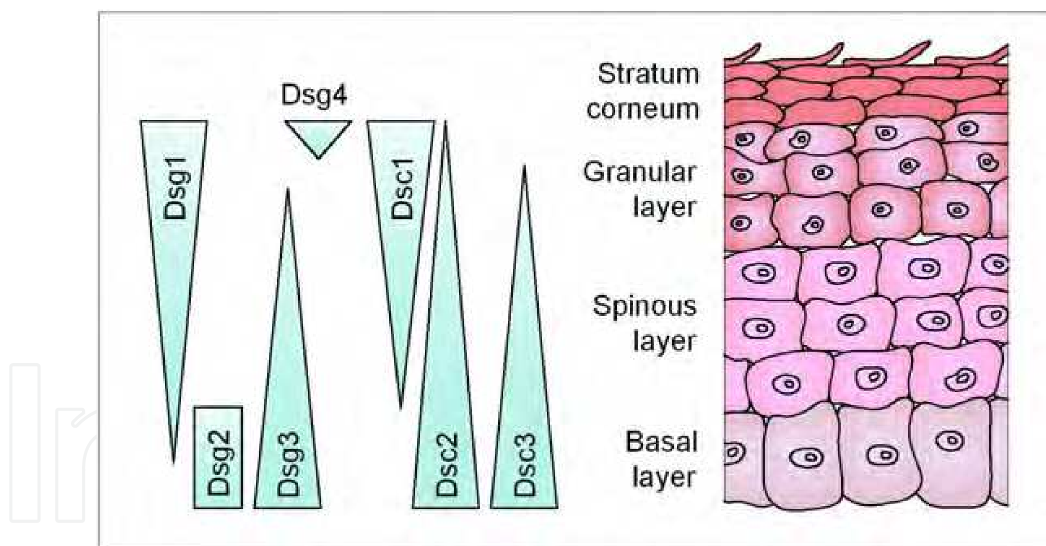

Fig. 2. Pattern of expression of desmogleins and desmocollins in normal human epidermis

Hair follicles exhibit morphological and ontogenic continuity with the epidermis. The distribution of DSGs in hair follicles (Fig. 3) has been described in some studies. Similar to epidermis, hair follicle is compartmentalized into a hierarchy of cells types based on the level of differentiation (Wu et al., 2003). DSG1 is expressed in the inner root sheath, and the innermost layers of the outer root sheath. There is a report that DSG2 is highly expressed by the least differentiated cells of the cutaneous epithelium, including the hair follicle bulge of fetus and adult, bulb matrix cells, and basal layer of the outer root sheath (Wu et al., 2003). Expression of DSG3 in hair follicle is correlated with different types of keratinization (all

layers of outer root sheath in areas of trichilemmal keratinization and mainly the basal layer in areas of epidermal-like keratinization) (Wu et al., 2003). DSG4 is expressed specifically in hair shaft cortex, lower hair cuticle, and upper inner root sheath cuticle (Bazzi et al., 2009), what corroborated with findings based on *DSG4* mRNA obtained by Bazzi et al. (Bazzi et al., 2006). Probably this molecule is a key mediator of keratinocyte cell adhesion in hair follicle, where it coordinates the transition from proliferation to differentiation (Brennan et al., 2010). Analysis of expression of DSCs, with the use of monoclonal antibodies, in anagen hair follicles indicated that DSC1 is selectively localized in the inner root sheath. DSC2 is present in the area of cell borders of the central layer of the outer root sheath, while DSC3 shows increasing intensity with progressive differentiation (Kurzen et al., 1998).

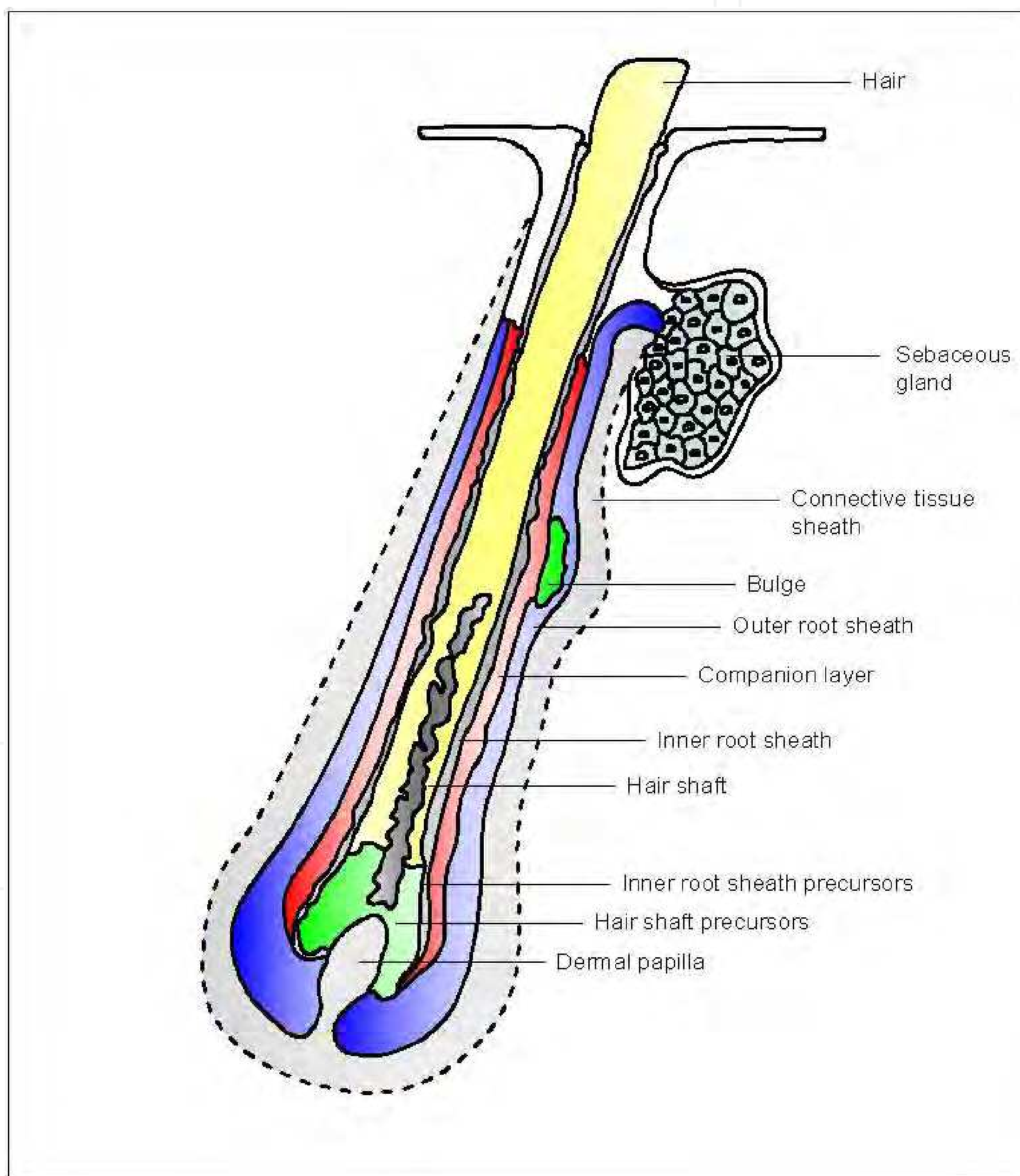

Fig. 3. Pattern of expression of desmogleins in normal human hair follicle. Desmogleins are marked as follows: red – DSG1, green – DSG2, blue – DSG3, yellow-DSG4

Recent studies have suggested that bulge region might be the reservoir of stem cells of hair follicles (Ma et al., 2004; Ohyama, 2007). Hair follicle stem cells are multipotent and having a superior clonogenicity and proliferative capacity. They are capable of giving rise to all cell types of hair, epidermis and sebaceous gland (Ma et al., 2004; Ohyama, 2007, Wu et al., 2003). Bulge cells might be susceptible to genetic alternation and be a source of carcinogenic mutations (Ohyama, 2007). Some data has suggested that several skin tumors, including BCC, might be derived from hair follicle cells, particularly from bulge cells (Ohyama, 2007). Most current data indicated (Grachtchouk et al., 2011) that probably there is a link between subtypes of BCC and its cell of origin, and constitutive hedgehog signaling activity.

3.2 Desmosomal cadherins and tumorigenesis

It is known that modulation or loss of intracellular junctions known as desmosomes has been implicated in tumorigenesis and contributes to the invasive and metastatic behavior of cancer cells (Teh et al., 2011). Beaudry et al. noted that probably desmosome loss does not promote tumorigenesis via a general trans-differentiation mechanism, but rather via more specific manner related to changes caused by complete desmosome-deficiency (Beaudry et al., 2010). However, studies about expression of desmosome components during human cancer progression have generated conflicting results (Beaudry et al., 2010). Thus, further genetic studies with animal models, such as knockout mice, to evaluate the functional consequence of desmosome alternation for tumorigenesis are necessary (Beaudry et al., 2010). Teh et al. found that downregulation of desmosomal components, particularly the DCs, precedes malignancy and is associated with desmosomal dysfunction (Teh et al., 2011). Beaudry et al. studying Perp-lacking mice demonstrated that Perp-deficiency indeed leads to accelerated skin tumorigenesis and PERP protein may be important as a tumor suppressor in humans (Beaudry et al., 2010).

Findings obtained by Teh et al. indicated that decreased assembly of desmosomes or down-regulation of desmosomal proteins, including DCs, is associated with several epithelial cancers (Teh et al., 2011). Studies on the role of DCs in BCC are relatively scanty in relation to squamous cell carcinoma (SCC), while it seems that BCC is the most common type of skin cancer. Better understanding of molecular basis of BCC may also lead to improvement therapeutic approaches. However, to the best of our knowledge, there have been no definitive data about the expression of all of DCs in BCC. Still, several reports (Mahoney et al., 2010; Bazzi & Christiano, 2007) indicated that the expression of DCs in tumor cells may be associated with the invasive or metastatic ability of various skin carcinomas, including BCC (Gornowicz et al., 2009). Although the mechanism by which DCs affect the tumorigenesis has not be fully elucidated and require further investigation (Tada et al., 2000). Consequently, the cell-cell adhesions of BCC represent an interesting field of examination (Moll et al., 1997).

Elegant study showed that, in SCC, during desmosome assembly, DSG3 first forms simple clusters at the cell surface (Garrod et al., 2002). Then the incorporation of desmosomal cadherin into the desmosomes was isoform-dependent (Ishii et al., 2001). Probably DSG2 and DSG3 were incorporated, but DSG1 and DSC1a were not. DSG1 normally expressed in the upper layers of epidermis, so the importance of a differentiation program for expression was stressed (Ishii et al., 2001).

Electron microscope studies of BCC revealed a significant reduction of desmosomes compared with normal basal cells and hair follicle keratinocytes (Krunic et al., 1997). Dysfunction or loss of desmosomal cadherins are also possible events in the BCC and these events may precede overt malignancy.

3.2.1 Expression of desmosomal cadherins in BCC

The desmosomal immunostainig (plakophilin 1) observed in BCC was very heterogeneous: in general, junctions in well-differentiated stratified tumor regions were more intensely stained than sections of poorly differentiated and invasively growing BCCs (Moll et al., 1997)

Tada et al. using immunofluorescence with monoclonal antibody revealed that expression of DSG1 in BCC was decreased or absent in tumor cells, whereas the expression of E-cadherin was strongly positive (Tada et al., 2000). Moreover, all of examined by Tada et al. (Tada et al. 2000) BCC cases showed no metastasis, then it is suggested that E-cadherin but not DCs may prevent the detachment of tumor cells from tumor nests. Bazzi et al. (Bazzi & Christiano, 2007) indicated that the links between classical cadherin (such as E-cadherin) downregulation and metastasis through epithelial–mesenchymal transition are well established. However, they noticed that still it remains to be determined whether a similar link between desmosomes and cancer exists and if so, which desmosomal components are involved (Bazzi & Christiano, 2007).

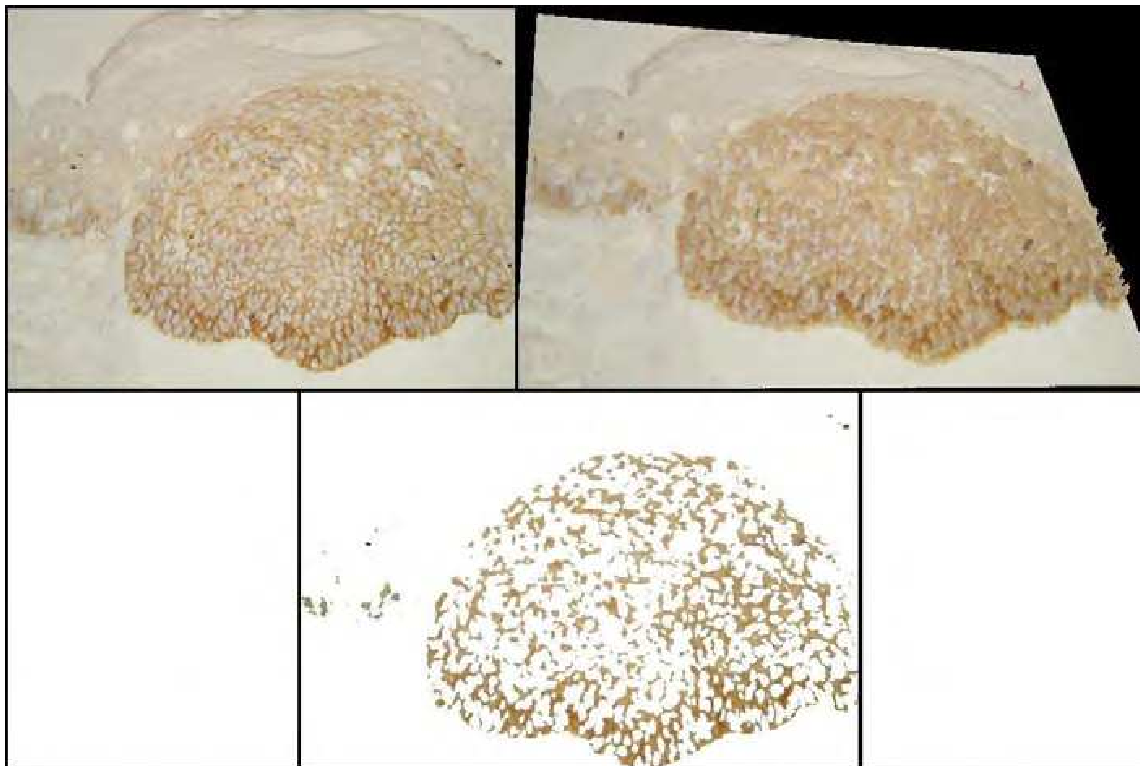

Fig. 4. Expression of DSG2 in BCC nests in patient with BCC. DSG2 expression in immunohistochemistry (top left) (immunoperoxidase staining on frozen sections), DSG2 expression processed with digital microscopic image analysis superimposed on DSG2 expression in immunohistochemistry (top right), intensity of DSG2 expression processed with digital microscopic image analysis (bottom) (original magnification x400).

It is suggested that only DSG2 may be found in tumors whereas the synthesis of other DSGs is much restricted. This hypothesis was corroborated by Schafer, who detected DSG2 in carcinoma cells with immunohistochemistry. Increased level of DSG2 in BCC was also observed in further investigation (Brennan & Mahoney 2009; Gornowicz et al., 2009). Brennan et al. identified DSG2 as a potential new marker for epithelial-derived malignancies and postulated that overexpression of DSG2 may deregulate multiple signaling pathways associated with increased growth rate, anchorage-independent cell survival, and the development of skin tumors (Brennan & Mahoney, 2009). In light of this, DSG2 overexpression may activate signal transduction pathways such as PI3K/Akt, MAPK, STAT3 and NFkappaB, which are often involved in cell proliferation and survival (Brennan & Mahoney, 2009). This group of researchers also noticed that the current dogma in cancer biology is that cell adhesion is reduced during malignant transformation, in turn allowing malignant cells to migrate, invade and metastasize. These data are compatible with our results (Bowszyc-Dmochowska et al., 2010, 2011), which demonstrated, with quantitative digital morphometry, an increased expression of DSG2 in BCC nest compared to normal epidermis (Fig. 4, Fig. 5). Furthermore, we found a significant correlation (r=+0.6092) between intensities of DSG2 and DSG3 expression in normal epidermis, but no significant correlation between those markers in BCC. However, still the potential value of DSG2-specific antibodies in tumor diagnosis as well as in studies of the mechanisms desmosomal cell coupling is discussed (Schäfer et al., 1996).

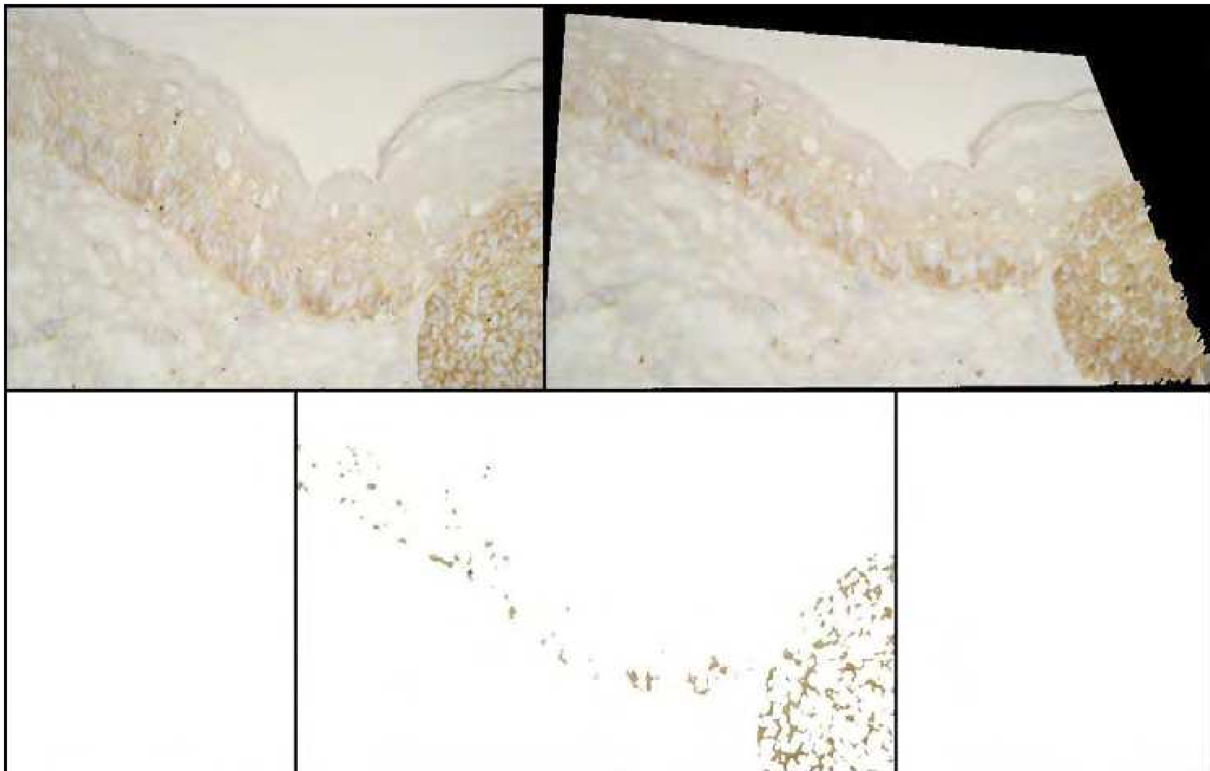

Fig. 5. Expression of DSG2 in non-BCC-affected epidermis. DSG2 expression in immunohistochemistry (top left) (immunoperoxidase staining on frozen sections), DSG2 expression processed with digital microscopic image analysis superimposed on DSG2 expression in immunohistochemistry (top right), intensity of DSG2 expression processed with digital microscopic image analysis (bottom) (original magnification x400).

The studies on the expression of DSG3 in human tumors are still scarce. Hence, the role and mechanism of DSG3 in cancer development remain to be elucidated. Study on expression of DSG3 in BCC (Gornowicz et al., 2009), using mathematical analysis of immunoperoxidase staining images, revealed that DSG3 expression is significantly decreased in BCC nest compared to both BCC-free epidermis in BCC patients (Fig. 6, Fig. 7) and patients with more benign tumors than BCC. Thus, these results seem to indicate that DSG3 might be involved in BCC pathogenesis as its decreased expression in BCC-affected epidermis might be responsible, in part, for locally invasive behavior of that tumor. The intriguing question arises what causes this decrease of expression of DSG3 in BCC, in other words whether it is a cause or result or somehow both of perturbed adhesion in BCC. It is noticed (Gornowicz et al., 2009) that the cooperation of p53/Perp (Kanellou et al., 2009; Bektas & Rubenstein 2009) pathways with DSG3 in regulating/disturbing keratinocyte adhesion in BCC is a sheer speculation at present, but this should be experimentally verified, especially as a role for Perp in DSG3-linked pemphigus vulgaris has recently been postulated (Nguyen et al., 2009). Alternatively, an exciting possibility is, giving the fact that tightly packed cancer cells showing a palisade arrangement on the periphery of the tumor are characteristic for BCC (Lever & Schaumburg-Lever, 1990), that the diminution/lack of DSG3-mediated adhesion is not enough for BCC cells to separate fully. In some cases of cancer the inhibition of tumor growth and invasion following the knockdown of DSG3 mediated by RNA interference (RNAi) was observed (Teh et al., 2011). RNAi is a powerful tool to dampen the level of proteins that are mutated or frequently overexpressed in skin diseases (Simpson et al., 2010). In BCC, perhaps, the DSG3 may be the target protein for RNAi.

There is no report on the involvement of DSG4 in BCC pathogenesis. Our own experiments using a commercially available anti-DSG4 antibody (unpublished data) with immunohistochemical staining, despite repetitive attempts under various conditions, gave no satisfying results. We found unequivocal DSG4 expression neither in BCC nests nor in normal epidermis, whereas DSG4 appeared to be expressed in sweat glands. It is known that BCC may show differentiation resembling the adnexal structures, such as hair follicles, sebaceous glands, or eccrine and apocrine sweat glands (Haushild et al., 2008). Interestingly, eccrine sweat glands are generally considered as a possible epidermal stem cell source (Biedermann et al., 2010). Birdermann described both *in vitro* and *in vivo* the capability of human eccrine sweat gland cells to form a stratified interfollicular epidermis. Little evidence for a sweat gland origin of the basal cell tumor has been presented by previous investigators (Zackheim, 1963). The origin of BCC from sweat gland ducts has been recorded, but probably its origin from sweat gland acini is extremely rare, if not actually unknown (Arnold, 1948). Still, a plausible link between DSG4 expression in sweat glands and BCC showing sweat gland-like structures should be explored.

Desmosomal and hemidesmosomal adhesion systems are downregulated in the hair matrix region of hair follicle and in BCC resulting from abnormal growth of developing hair follicles (Nanba et al., 2000). Some observation shown that the desmosomal adhesion system, in which the DCs of DSCs and DSGs function, is downregulated in hair placodes (Nanba et al., 2000). Furthermore, hair follicles, which physiologically express DSGs, apparently are involved in BCC pathogenesis (Gornowicz et al., 2009). Particularly, bulge cells are in the area of research interest, because of their possible role in tumorigenesis (Ohyama, 2007), including that of BCC. Several research groups have noted that some BCCs express K-15 that is usually expressed in human follicle bulge cells (Ohyama, 2007).

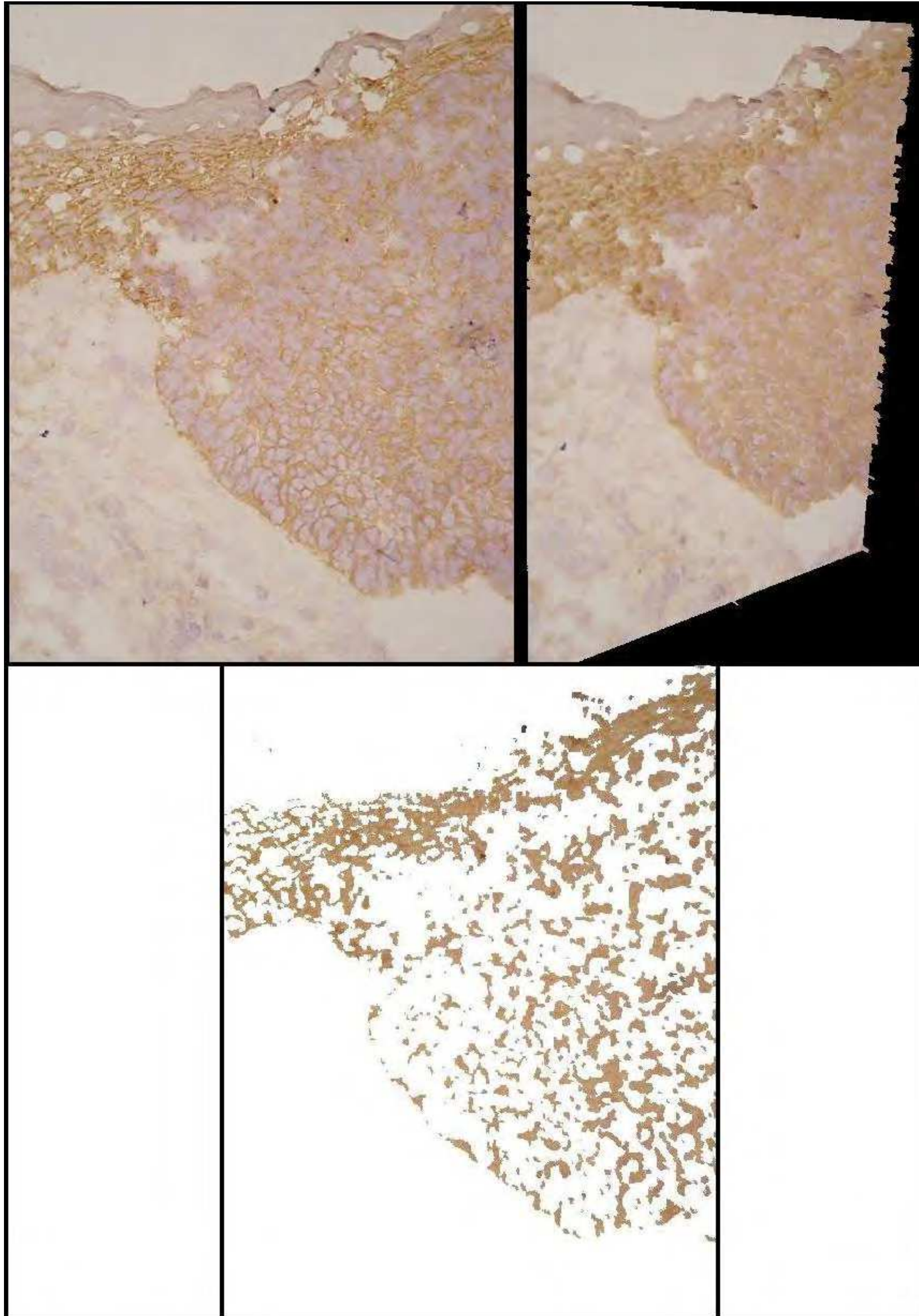

Fig. 6. Expression of DSG3 in BCC nests in patient with BCC. DSG3 expression in immunohistochemistry (top left) (immunoperoxidase staining on frozen sections), DSG3 expression processed with digital microscopic image analysis superimposed on DSG3 expression in immunohistochemistry (top right), intensity of DSG3 expression processed with digital microscopic image analysis (bottom)
(original magnification x400).

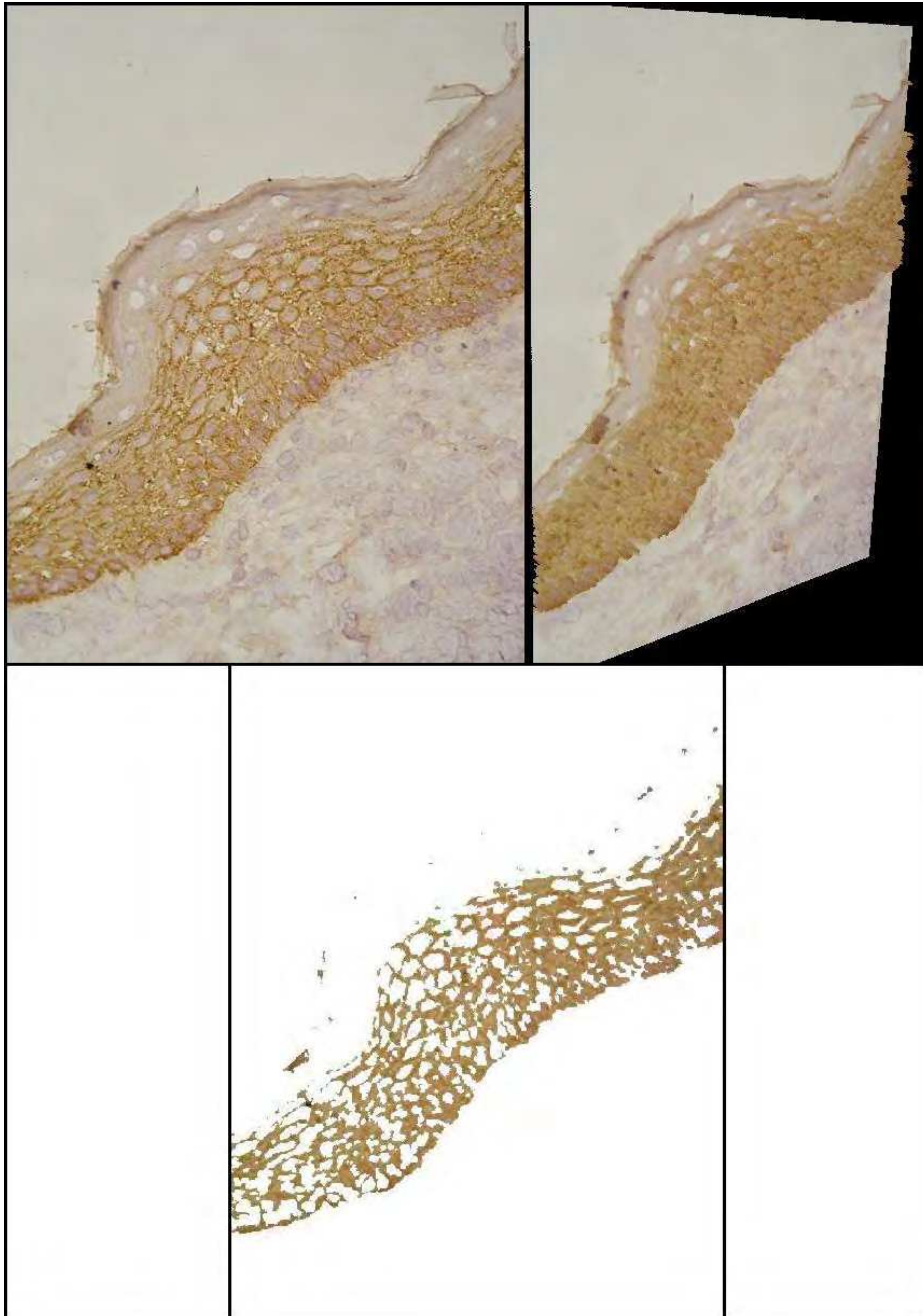

Fig. 7. Expression of DSG3 in non-BCC-affected epidermis. DSG3 expression in immunohistochemistry (top left) (immunoperoxidase staining on frozen sections), DSG3 expression processed with digital microscopic image analysis superimposed on DSG3 expression in immunohistochemistry (top right), intensity of DSG3 expression processed with digital microscopic image analysis (bottom)
(original magnification x400).

Interestingly, it has been found that overexpression of *Shh* gene (sonic hedgehog), a gene essential for hair follicle morphogenesis, resulted in the formation of BCC like tumors (Ohyama, 2007). However, Youssef et al. using murine model (Youssef et al., 2010) have very recently revealed that BCC does not originate from bulge stem cells, as previously thought. With the use of clonal analysis they have found using mouse model of the disease that BCC arises from long-term resident progenitor cells of the interfollicular epidermis and the upper infundibulum (Youssef et al., 2010). Still, DSGs can be important in BCC pathogenesis regardless of the issue of BCC cellular origins as they are expressed in both bulge region and the upper infundibulum of hair follicle and interfollicular epidermis (Gornowicz et al., 2009).

Overall, what noticed Chidgey (Chidgey & Dawson, 2007), findings obtained by different authors demonstrate that alterations in DCs expression patterns, perhaps through modified intracellular signalling and/or changes in adhesive strength, have fundamental effects on cell behaviour, and can in some situations drive proliferation (Chidgey & Dawson, 2007). Thus, alterations in the expression of DCs in cancer could result in the release of plakoglobin from desmosomes, subsequent displacement of β-catenin from adherens junctions and increased Wnt/β-catenin signaling (Chidgey & Dawson, 2007).

3.3 Alternative splicing of DCs and tumorigenesis in BCC

Alternative splicing (AS) generates mRNA that encodes different polypeptides from a single gene. Different protein isoforms of a single gene may have distinct or even antagonistic functions, due to the insertion or deletion of key functional regions (Xing, 2007). AS is a common phenomenon and more than 90% human genes are alternatively spliced (Pan et al., 2008; Wang et al., 2008). It is known that AS is involved in numerous human diseases (Kim et al., 2007), thus accumulating evidence revealed that aberrant splicing contributes to human neoplasms (Miura et al, 2011; Xing, 2007; Kim et al., 2007; Venables, 2006; He et al., 2007; Srebrow & Kornblihtt, 2006). However, in only few cases it has been proved, e.g. breast and ovarian cancer, prostate cancer (Lixia et al., 2007; Rohlfs et al., 2000; Thorsen et al., 2008; Rajan et al., 2009). Kim et al. shown that cancerous tissues exhibit lower levels of AS than do normal tissues, what might be a result of disruption of splicing regulatory proteins (Kim et al., 2007).

AS is a fundamental molecular process which generates proteome functional diversity and may play a significant role in cell differentiation and proliferation, probably through the production of alternative transcripts of DCs. Srebrow et al. (Srebrow & Kornblihtt, 2006) indicated that the connection between the signaling pathways and splicing regulation can lead to the deregulation of proliferation and differentiation, which may contribute to cancer. The discovery of the events of AS in the DCs transciptome of BCC cells and understanding how AS contributes to tumorigenesis (Xing, 2007) may produce new medical implications, e.g. drug targets. However, the knowledge about AS in BCC is still limited. Some reports indicate that alternative splicing pattern of Mcl-1 (myeloid cell leukemia 1) may induce apoptosis in BCC (Shieh et al., 2009).

Both DSGs and DSCs exist in multiple isoforms (Hardman 2004). It is known that DSCs occur as “a” and “b” splice variants (Hardman et al., 2004; Cheng et al., 2003) and these alternative transcripts have different function. The “a” variant having slightly longer cytoplasmic domain can support desmosomal assembly (Hardman et al., 2004; Cheng et al., 2003). Some hypothesis indicate that “b” form mediates or regulates DSC signaling activity

through its distinct cytoplasmic domain; however, Hardman et al. observed that DSC3b may be involved in epidermal differentiation regulation (Hardman et al., 2004).
Recent work revealed that the expression of DCs might be altered in cancers originating from keratinocytes (Lee et al., 2009). Lee et al. (Lee et al., 2009) examined expression of splicing variant of DSG3 in epidermal cancers, such as SCC and BCC. Their expression was highly increased in SCC, but not in BCC. These results suggest that splicing variant of DSG3 may disturb desmosome assembly components and weaken the cell-cel interaction (Lee et al., 2009). Thus, AS of DCs may affect signaling in the cell and regulate process of epidermal differentiation and proliferation.
Searching NCBI Gene Database by DSGs names revealed interesting issues. In humans, only *DSG4* gene is described as having alternative splicing form (DSG4 isoform 1 and DSG4 isoform 2). Interestingly, there is no NCBI data about AS in *DSG1, DSG2* and *DSG3* genes. However, some researchers (Lee et al., 2009) suggested that AS may generate a splicing variant of DSG3 (ΔNDg3). Thus, these results shown that molecular analyses of DCs should still be considered an important research area. It should be remembered that correct interpretation of genetic alternation and the investigation of aberrant transcripts is crucial for genetic diagnosis and molecular characteristics of neoplasms (Miura et al., 2011), including BCC. In light of this, oligonucleotide microarrays containing exon junction probes may be a powerful tool to investigate tissue-specific regulation of AS taking place in BCC (Nagao et al., 2005). Literature data may suggest that AS should be regarded as a potential source for new clinical diagnostic, prognostic and therapeutic strategies in cancer (He et al., 2007).

4. Conclusions

Thus, it seems that DCs might be involved in BCC pathogenesis. Seemingly, the expressions of DSG2 and DSG3, adhesion molecules that plausibly play different roles in proliferation and differentiation of epidermis, are coordinated in normal epidermis, but this apparent coordination is lost in BCC. That loss of coordination of DSG2 and DSG3 expressions, revealed with quantitative digital morphometry, in BCC might be a partial explanation of BCC behaviour as a locally invasive tumor.
There is still a very interesting issue, what role desmosomal adhesion and desmosomal components (particularly DSGs) play in carcinogenesis. The disturbance of desmosomal adhesion can result in tissue integrity damage and possibly induction of tumor cell migration and proliferation. Study on the role of DSG in BCC may suggest that in human skin DSG2-mediated adhesion appears to be more proliferation-associated, whereas DSG3-mediated adhesion seemingly is more differentiation-associated.
The impact of signaling pathway, involving DCs mediated adhesion, and cells of origin for BCC on different subtypes of BCC should be explained. Work with murine model, which was carried out by Grachtchouk et al. (Grachtchouk et al., 2011), shown that the level of expression of constitutive hedgehog pathway effector (GLI2*) is depended on histological BCC subtypes. Moreover, they indicated that phenotype of BCC may be determined by the cell of origin and tissue context. Thus, these connections may determine the different biological behavior of BCC.
Progress in these areas will lead to a better understanding of the role of desmosomes in normal tissue homeostasis and malignancy (Chidgey & Dawson, 2007).

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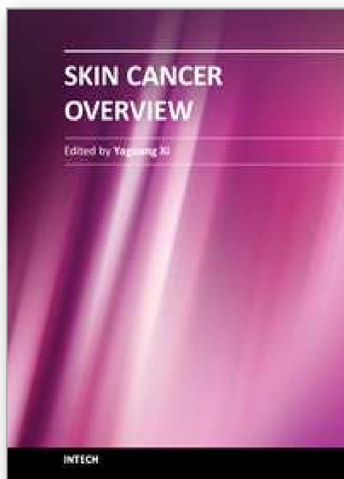

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The book Skin Cancer Overview is divided into three sections to cover the most essential topics in skin cancer research: Etiology, Diagnosis and Treatment, and Prevention. Due to the complexity of skin cancer, this book attempts to not only provide the basic knowledge, but also present the novel trends of skin cancer research. All chapters were written by experts from around the world. It will be a good handbook for researchers with interests in skin cancer.

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