Chapter 5

Cadherins and their Role in Malignant Transformation: Implications for Skin Cancer Progression

Marcelina E. Janik, Dorota Hoja-Łukowicz and Małgorzata Przybyło

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/64666

Abstract

Cadherins are a large family of Ca^{2+}dependent adhesion proteins. They are transmembrane or closely related to membrane glycoproteins localized in specialized adhesive junction. The expression of various cadherins may be concomitant with cancer progression steps and the term 'cadherin switch' has been created due to the observation of down-regulation of E-cadherin (suppressor of metastatic potential) and up-regulation of N-cadherin (promoter of metastatic potential) expression during tumour progression. These changes are thought to be closely related to epithelial-to-mesenchymal transition of cells of many different types of cancer including skin cancers, and accompany the increase of their motility and invasion abilities resulting in the metastasis formation. The cadherin polypeptide is a potential substrate for post-translational modification, for example, N-glycosylation, and its important role in the regulation of cadherin function has been described. The changed glycosylation of cadherins has been described in various skin cancers including melanoma and was consistent with cadherins' role in epithelial-to-mesenchymal transition. The detailed analysis of cadherin expression and cadherin-related glycosylation changes taking place during malignant transformation could be a key for better understanding of the nature of this process and may open new opportunities for the creation of more effective anticancer therapeutics and diagnostic tools.

Keywords: cadherins, melanoma, basal cell carcinoma, squamous cell carcinoma, glycosylation, metastasis

1. Introduction

In humans, cadherins comprise a superfamily of over 100 calcium-dependent adhesion molecules that play fundamental roles in supervising morphogenetic and differentiation processes during development, and in maintaining tissue architecture and homeostasis [1]. Therefore, their expression is tightly regulated during development, and abnormalities in the expression or function of cadherins are characteristic features of transformed cells. Being transmembrane proteins, cadherins are built from extracellular, transmembranous and cytoplasmic domains. The only exception is an unusual T (truncated)-cadherin, which is similar to the classical cadherins in terms of ectodomain construction, but differs from them by lacking both the transmembrane and cytoplasmic domains. Instead, T-cadherin is linked to plasma membrane through a glycosylphosphatidylinositol (GPI) anchor [2]. Extracellular domain of T-cadherin lacks many amino acids, which are responsible for the adhesive function of the classical cadherins. Therefore, it is suggested that T-cadherin functions as a signalling molecule rather than as a cell adhesion molecule [3].

According to the sequence similarity, cadherins have been divided into five subfamilies: classical types I and II (E-, P-, N- and VE-cadherin), atypical (T-cadherin), desmosomal (desmogleins, desmocollins), protocadherins and cadherin-related proteins [4]. Cadherins maintain stable cell-cell adhesion via homophilic interactions of their extracellular regions that trigger the assembly of specialized adhesive junctions (AJs) known as desmosomes and adherens junctions, and tethering the microfilaments and intermediated filaments to the plasma membrane by the cytoplasmic domains [5]. In this way, cadherins, by mediating adhesion, provide a cohesion and communication between cells in a tissue [1]. The cytoplasmic region anchors cadherin to actin cytoskeleton via interaction with catenin family—β-catenin, γ-catenin, which binds directly to cadherin tail, and α-catenin, which links β- or γ-catenin to actin.

β-catenin is attached to cadherin in the endoplasmic reticulum at the early stage of its targeting to the plasma membrane, where they are present as a complex. Therefore, this cadherin-β-catenin interaction is independent of cadherin engagement in adhesion [6]. α-catenin has been perceived as a constituent stably binding the β-catenin-cadherin complex to actin cytoskeleton, but it has been shown nowadays that allosteric character of α-catenin indisposes its binding to β-catenin and F-actin at the same time [7]. Another member of the catenin family, p120-catenin, attaches to the cadherin-catenin complex in the plasma membrane and controls cadherin turnover by stabilization of the complex assembly at the plasma membrane. p120-catenin knockdown experiments with the use of RNAi have shown a more rapid turnover and degradation of cadherin complexes [8]. β-catenin and p120-catenin are substrates of tyrosine kinase receptor, and therefore the adhesion could be regulated by the action of growth factors [9]. Clustering of AJs results in remodelling of the actin cytoskeleton [10–13]. There is a wide variety of proteins associated with cadherins and this association is thought to be transient and adjustable dependent on cell context and the triggered cellular-signalling pathways [14].

First reports of Ca^{2+}-dependent surface glycoproteins mediating intercellular adhesion have regarded chick development and process of morula compaction in pre-implantation mouse

http://dx.doi.org/10.5772/64666

embryo [15–18]. The first identified, E-cadherin is a classical type I cadherin, and its prefix 'E' refers to the epithelial cells (ECs) where it was originally described. Other classical cadherins of a different spatiotemporal expression pattern include N-cadherin (neural, type I), P-cadherin (placenta, type I) [19], R-cadherin (retina, type I) [20] and VE-cadherin (vascular endothelial, type II) [21].

The structure of classic cadherin molecules is more or less conserved; they possess a cytoplasmic domain associated with the armadillo proteins family [22], and in the case of E-cadherin this region comprises 150 aa [4]. Next, there is a single-pass transmembrane region, and extracellular domain of 550 aa, which in classic cadherins (types I and II), desmosomal and T-cadherin contain five segments of a repeated sequence. The extracellular domains are numbered from EC1 to EC5, where the sequence of the headmost EC5 is characteristic because of the presence of four conserved cysteine residues [4, 23, 24]. In the extracellular domain between the adjacent EC domains, the highly conserved Ca^{2+}-binding sequences are located.

Based on E-cadherin structure analysis, several possible mechanisms of cadherin-mediated cell-cell adhesion have been proposed. Cadherins could form either *trans* dimers, where the linkage is formed by cadherins from apposed cells, or *cis* dimers, where the lateral interaction between cadherin molecules in the same cell membrane takes place. Their formation depends on Ca^{2+} availability. In Ca^{2+} presence, *trans* dimers are formed preferentially, while in its absence *cis* dimer formation predominates. Furthermore, *trans* dimers are thought to be responsible for cell-cell adhesion, and the formation of *cis* dimers has been reported to enhance the strength of adhesive interaction [11, 25]. Both dimers are formed via the same region of cadherin molecules—EC1 domain; however, the involvement of EC3 domain has also been confirmed in the case of *trans* dimerization process. Concerning EC1 and EC3 role in *trans* dimerization, three possible adhesive antiparallel alignments have been proposed, starting from the outermost adhesive bonds between EC1 domains, through middle bond requiring both EC1 and EC3 contribution in bond formation, and finally the innermost adhesive bounds formed by the EC3 domains [26]. The classic model assumed that there are homophilic interactions between cadherins, but growing evidence suggests also the presence of heterophilic ones. Shan and co-workers have reported heterophilic interactions between R- and N-cadherins interacting either in *cis* or in *trans* manner [25]. Importantly, cadherins can be post-translationally modified by phosphorylation, O-glycosylation but the most prominent modification is N-glycosylation [10, 27–29].

2. Cadherins and skin cancers

It is well known that the transformation of normal tissue cells to tumour cells is associated with the changes in the repertoire of cell-surface adhesions, such as cadherins, and carbohydrate structures are attached to them. Altered glycosylated cell-surface glycoproteins influence the growth, proliferation and survival of tumour cells, and facilitate their migratory and invasion behaviour, formation of distant metastases as well as the induction of immunosuppression. It is noteworthy that tumour-associated antigens can serve as valuable diagnostic and therapeutic targets.

Skin tumours comprise melanoma and non-melanoma skin cancers. Non-melanoma neoplasms are mainly divided into basal cell carcinoma (BCC), squamous cell carcinoma (SCC), keratoacanthoma (KA, a benign low-grade skin tumour without the competence to metastasize or invade), trichoepithelioma (TE, a benign skin tumour, which arises from the hair germ), actinic keratosis (AK, a precancerous stage of squamous cell carcinoma) and Merkel cell carcinoma (MCC, an early metastasizing neoplasm of high-grade malignancy). Although melanoma is much less common, it possesses high potential to invade surrounding tissues and very quickly develops distant metastases. Therefore, melanoma is the leading cause of deaths from skin cancer.

2.1. Cadherins in the skin

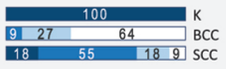
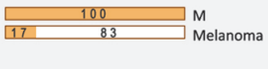
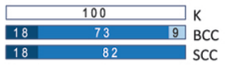
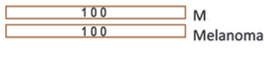
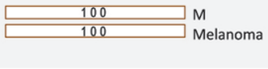
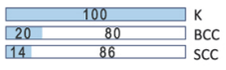
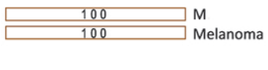
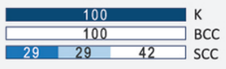
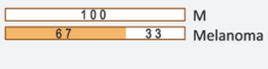
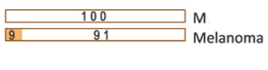
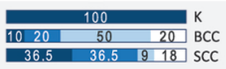
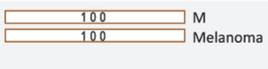
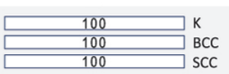
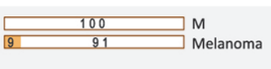
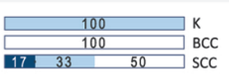
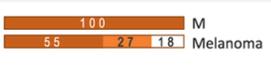
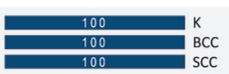
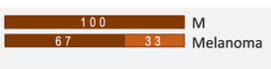
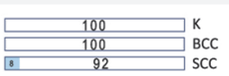
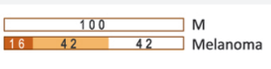
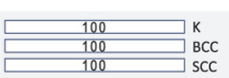
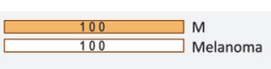
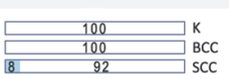
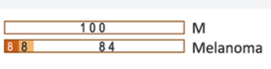
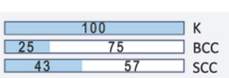
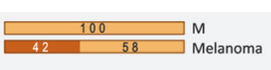
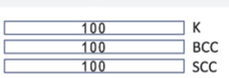
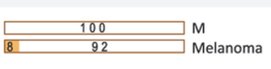
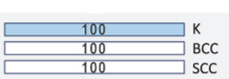
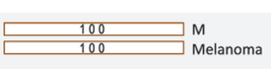
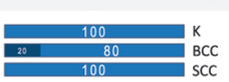
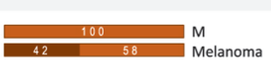
In human skin, the expression of several cadherin molecules, belonging to all five major groups of the cadherin family, has been described. The changes in their protein levels have been extensively investigated regarding the developmental processes and neoplastic transformation of skin cells (**Table 1**). The vast majority of research studies concern classical cadherins. Both E- and P-cadherins are the major components of the intercellular AJs of the epidermis [30], and they are main players in morphogenesis and in maintaining the structure of the skin. Referring to E-cadherin, the wide distribution of its expression in all skin layers and in skin appendages has been shown, and its role in keratinocytes-melanocytes adhesion and communication has been established. It has been reported that E- and N-cadherin-negative dermal stem cells (DSCs), isolated from human foreskin dermis during their differentiation into melanocytes and migration to the epidermis, gain E-cadherin expression, enabling them to interact with the keratinocytes [31]. On the other hand, *in vitro* experiments in melanocytes and keratinocytes co-cultures have shown that during wound healing and re-pigmentation process, diminished E-cadherin expression in melanocytes increases their migration capacity as they migrate much faster than keratinocytes into the wound area [32].

The expression of P-cadherin, which is known to be indispensable for proper skin and eye function, has been more diversified and dependent on the skin layer. It is mainly present in the basal and lower suprabasal layers, where it was linked with the proliferative compartment of the epidermis. The predominant expression of P-cadherin has also been observed in the growing hair follicle, where it has an important role in its differentiation. Moreover, P-cadherin has been suggested to have a regulatory effect on melanogenesis, mainly due to the inhibition of tyrosinase activity, and to regulate melanosome transport within the melanosome unit [24].

The expression of N-cadherin has also been described in the skin during developmental processes, referring to dermal fibroblasts and endothelial cells but not in keratinocytes or melanocytes [33]. N-cadherin expression has been analysed in murine model of melanocytes development and *in vitro* cultured melanoblast, melanocyte and melanoma cell lines. The melanoblasts/melanocytes of a 3-day-old mouse dermis have expressed only small amount of N-cadherin, while its significantly higher expression has been reported in all *in vitro* models [34]. The changed expression of N-cadherin on dermal melanocytes has been suggested to enable their migration during developmental processes and stabilized their interaction with dermal fibroblasts [35].

http://dx.doi.org/10.5772/64666

Protein	Gen (location)	Protein expression level in cancer skin tissue [a]	Structure [b]
Type I classical cadherins			
Cadherin 1 (E-cadherin)	*CDH1* (16q22.1)	100 K; 23 57 20 BCC; 7 59 24 4 SCC; 100 M; 10 40 13 37 Melanoma	E-cadherin
Cadherin 2 (N-cadherin)	*CDH2* (18q12.1)	100 K; 8 92 BCC; 100 SCC; 100 M; 13 6 10 71 Melanoma	
Cadherin-3 (P-cadherin)	*CDH3* (16q22.1)	100 K; 18 82 BCC; 10 90 SCC; 100 M; 32 37 26 5 Melanoma	
Cadherin 4 (R-cadherin)	*CDH4* (20q13.33)	100 K; 100 BCC; 86 14 SCC; 100 M; 17 25 58 Melanoma	
Type II classical cadherins			
Cadherin 5 (VE-cadherin)	*CDH5* (16q21)	100 K; 60 40 BCC; 50 50 SCC; 100 M; 83 17 Melanoma	cadherin 11
Cadherin 6 (K-cadherin)	*CDH6* (5p13.3)	100 K; 47 53 BCC; 10,5 63 26,5 SCC; 100 M; 9 91 Melanoma	
Cadherin 7	*CDH7* (18q22.1)	100 K; 100 BCC; 100 SCC; 100 M; 9 91 Melanoma	
Cadherin 9 (T1-cadherin)	*CDH9* (5p14.1)	100 K; 20 80 BCC; 83 17 SCC; 100 M; 25 67 8 Melanoma	
Cadherin 11 (OB-cadherin)	*CDH11* (16q21)	100 K; 75 25 BCC; 100 SCC; 100 M; 17 83 Melanoma	
Cadherin 12 (N-cadherin 2)	*CDH12* (5p14.3)	100 K; 50 50 BCC; 17 50 33 SCC; 100 M; 33 33 34 Melanoma	
Cadherin 18	*CDH18* (5p14.3)	100 K; 100 BCC; 100 SCC; 100 M; 27 27 46 Melanoma	
Cadherin 19	*CDH19* (18q22.1)	100 K; 100 BCC; 12,5 87,5 SCC; 100 M; 8 92 Melanoma	
Cadherin 20	*CDH20* (18q21.33)	100 K; 100 BCC; 43 57 SCC; 100 M; 50 42 8 Melanoma	
Cadherin 22	*CDH22* (20q13.12)	100 K; 100 BCC; 14 86 SCC; 100 M; 27 27 46 Melanoma	
Truncated/atypical cadherin			
Cadherin 13 (H-cadherin , T-cadherin)	*CDH13* (16q23.3)	100 K; 23 73 BCC; 8 92 SCC; 100 M; 100 Melanoma	T-cadherin

Protein	Gen (location)	Protein expression level in cancer skin tissue[a]	Structure[b]
Desmosomal cadherins			
Desmoglein 1	*DSG1* (18q12.1)		
Desmoglein 2	*DSG2* (18q12.1)		
Desmoglein 3	*DSG3* (18q12.1)		
Desmoglein 4	*DSG4* (18q12.1)		
Desmocollin 1	*DSC1* (18q12.1)		
Desmocollin 2	*DSC2* (18q12.1)		
Desmocollin 3	*DSC3* (18q12.1)		
Protocadherins clustered			
Protocadherin α 1	*PCDHA1* (5q31.3)		
Protocadherin α 2	*PCDHA2* (5q31.3)		
Protocadherin α 3	*PCDHA3* (5q31.3)		
Protocadherin α 5	*PCDHA5* (5q31.3)		
Protocadherin α 8	*PCDHA8* (5q31.3)		
Protocadherin α 12	*PCDHA12* (5q31.3)		
Protocadherin β 1	*PCDHB1* (5q31.3)		
Protocadherin β 2	*PCDHB2* (5q31.3)		
Protocadherin β 3	*PCDHB3* (5q31.3)		
Protocadherin β4	*PCDHB4* (5q31.3)		

Desmoglein 2

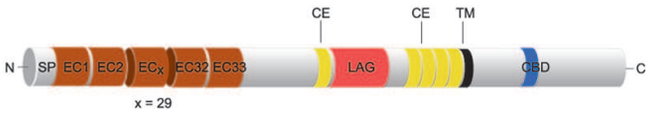
Protocadherin β 1

http://dx.doi.org/10.5772/64666

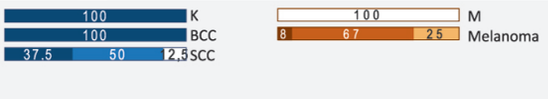
Protein	Gen (location)	Protein expression level in cancer skin tissue[a]	Structure[b]
Protocadherin β 5	*PCDHB5* (5q31.3)	K: 100; BCC: 100; SCC: 9 91	M: 100; Melanoma: 33 50 27
Protocadherin β 6	*PCDHB6* (5q31.3)	K: 100; BCC: 20 80; SCC: 14 86	M: 100; Melanoma: 25 75
Protocadherin β 7	*PCDHB7* (5q31.3)	K: 100; BCC: 100; SCC: 2,5 75 12,5	M: 100; Melanoma: 12,5 50 37,5
Protocadherin β 8	*PCDHB8* (5q31.3)	K: 100; BCC: 100; SCC: 100	M: 100; Melanoma: 18 64 18
Protocadherin β 9/10	*PCDHB9/10* (5q31.3)	K: 100; BCC: 30 40 30; SCC: 28,5 50 21,5	M: 100; Melanoma: 17 50 33
Protocadherin β 11/12	*PCDHB11/12* (5q31.3)	K: 100; BCC: 50 50; SCC: 50 50	M: 100; Melanoma: 83 17
Protocadherin β 14	*PCDHB14* (5q31.3)	K: 100; BCC: 33 67; SCC: 100	M: 100; Melanoma: 17 83
Protocadherin β 15	*PCDHB15* (5q31.3)	K: 100; BCC: 30 20 50; SCC: 25 33 42	M: 100; Melanoma: 10 90
Protocadherin γ subfamily A, 1	*PCDHGA1* (5q31.3)	K: 100; BCC: 40 60; SCC: 17 83	M: 100; Melanoma: 18 64 9 9
Protocadherin γ subfamily B, 3	*PCDHGB3* (5q31.3)	K: 100; BCC: 33 67; SCC: 67 33	M: 100; Melanoma: 8 25 67
Protocadherins nonclustered δ1			
Protocadherin 1	*PCDH1* (5q31.3)	K: 100; BCC: 43 57; SCC: 44 12 44	M: 100; Melanoma: 45,5 54,5
Protocadherin 7	*PCDH7* (4p15.1)	K: 100; BCC: 100; SCC: 43 43 14	M: 100; Melanoma: 27 64 9
Protocadherin 9	*PCDH9* (13q21.32)	K: 100; BCC: 100; SCC: 100	M: 100; Melanoma: 8 17 75
Protocadherin 11 X/Y-linked	*PCDH11X/Y* (Xq21.31/ Yp11.2)	K: 100; BCC: 100; SCC: 17 83	M: 100; Melanoma: 8 25 67
Protocadherins nonclustered δ2			
Protocadherin 8	*PCDH8* (13q14.3)	K: 100; BCC: 25 25 50; SCC: 17 17 66	M: 100; Melanoma: 46 27 27
Protocadherin 10	*PCDH10* (4q28.3)	K: 100; BCC: 25 50 25; SCC: 100	M: 100; Melanoma: 17 42 41

Protocadherin 1

Protocadherin 8

Protein	Gen (location)	Protein expression level in cancer skin tissue[a]	Structure[b]
Protocadherin 17	*PCDH17* (13q21.1)	K: 100 / BCC: 20, 60, 20 / SCC: 43, 28.5, 28.5 — M: 100 / Melanoma: 17, 50, 33	
Protocadherin 18	*PCDH18* (4q28.3)	K: 100 / BCC: 40, 60 / SCC: 57, 43 — M: 100 / Melanoma: 58, 42	
Protocadherin 19	*PCDH19* (Xq22.1)	K: 100 / BCC: 100 / SCC: 100 — M: 100 / Melanoma: 8, 8, 84	
Cadherin-releted proteins			
Cadherin-related 23	*CDH23* (10q22.1)	K: 100 / BCC: 66, 34 / SCC: 33, 33, 34 — M: 100 / Melanoma: 9, 73, 18	FAT atypical cadherin 1
Dachsous cadherin-related 1	*DCHS1* (11p15.4)	K: 100 / BCC: 44, 44, 12 / SCC: 8, 92 — M: 100 / Melanoma: 90, 10	
Dachsous cadherin-related 2	*DCHS2* (4q31.3)	K: 100 / BCC: 40, 40, 20 / SCC: 100 — M: 100 / Melanoma: 58, 8, 17, 17	
Cadherin 26	*CDH26* (20q13.33)	K: 100 / BCC: 100 / SCC: 100 — M: 100 / Melanoma: 8, 92	
Cadherin-related family member 1	*CDHR1* (10q23.1)	K: 100 / BCC: 100 / SCC: 14, 86 — M: 100 / Melanoma: 27, 73	
Cadherin-related family member 2	*CDHR2* (5q35.2)	K: 100 / BCC: 100 / SCC: 100 — M: 100 / Melanoma: 100	
Cadherin-related family member 4	*CDHR4* (3p21.31)	K: 100 / BCC: 17, 33, 50 / SCC: 17, 17, 59, 16 — M: 100 / Melanoma: 92, 8	
Protocadherin 12 (VE-cadherin-2)	*PCDH12* (5q31.3)	K: 100 / BCC: 100 / SCC: 14, 86 — M: 100 / Melanoma: 36, 36, 28	
FAT atypical cadherin 1	*FAT1* (4q35.2)	K: 100 / BCC: 58, 42 / SCC: 18, 46, 36 — M: 100 / Melanoma: 44, 44, 12	
FAT atypical cadherin 3	*FAT3* (11q14.3)	K: 100 / BCC: 100 / SCC: 83, 17 — M: 100 / Melanoma: 100	
FAT atypical cadherin 4	*FAT4* (4q28.1)	K: 100 / BCC: 100 / SCC: 17, 83 — M: 100 / Melanoma: 27, 73	
Calsyntenin 1	*CLSTN1* *1 p36.22*)	K: 100 / BCC: 60, 40 / SCC: 14, 86 — M: 100 / Melanoma: 36, 27, 27, 10	
Calsyntenin 2	*CLSTN2* (3q23)	K: 100 / BCC: 60, 40 / SCC: 14, 86 — M: 100 / Melanoma: 11, 89	
Calsyntenin 3	*CLSTN 3* (12p13.31)	K: 100 / BCC: 33, 67 / SCC: 37.5, 62.5 — M: 100 / Melanoma: 8, 17, 17, 58	
Ret proto-oncogene	*CRET* (10q11.21)	K: 100 / BCC: 37, 25, 19, 19 / SCC: 33, 11, 23, 33 — M: 100 / Melanoma: 33, 67	

http://dx.doi.org/10.5772/64666

Protein	Gen (location)	Protein expression level in cancer skin tissue[a]	Structure[b]
Cadherin, EGF LAG seven-pass G-type receptor 2	*CELSR2* (1p13.3)		
Cadherin, EGF LAG seven-pass G-type receptor 3	*CELSR3* (3p21.31)		

[a]Antibody staining/cadherin expression level in human keratinocytes, BCC, SCC and in human melanocytes and melanoma cells, respectively, described by the colour-coding scales: ■/■ high, ■/■ medium, ■/■ low, □/□ not detected. The numbers within bars correspond to the percentage of a given staining/cadherin expression level. Data for protocadherins γ 2-12 of subfamily A, protocadherins γ 1,2,4-7 of subfamily B and protocadherins γ 3-5 of subfamily C have not been analysed due to the antibodies that cross-reacted with multiple isoforms. Data are based on The Human Protein Atlas (www.proteinatlas.org).

[b]Schematic structure of a representative member of the given cadherin subfamily.

BCC, basal cell carcinoma; K, keratinocyte; M, melanocyte; and SCC, squamous cell carcinoma; C, COOH terminus of protein; CBD, β-catenin-binding domain or plakoglobin-binding domain in the case of desmosomal cadherins; CE, cysteine-rich EGF-repeat-like domain; CM1-3, conserved motifs in the cytoplasmic domains of nonclustered δ-protocadherins; EC, extracellular cadherin repeats; GPI, glycosylphosphatidylinositol anchor; JMD, juxtamembrane domain with p120-catenin-binding site; LAG, laminin-A globular domain-like domain; N, NH_2-terminus of protein; ProP, propeptide; RUD, intracellular repeated unit domain of desmosomal cadherins; SP, signal peptide; TM, transmembrane domain; and UCD, unique cytoplasmic domain.

Table 1. Comparison of the expression pattern of cadherins in keratinocytes versus BCCs and SCCs, and melanocytes versus melanoma cells.

In normal skin, the expression of T-cadherin is mostly limited to melanocytes and actively proliferating keratinocytes of the basal layer, as well as to a lesser extent to dermal blood vessels. Unlike other cadherins, T-cadherin molecules are anchored in lipid rafts dispersed on the whole cell plasma membrane [36].

The changes in the expression level of particular cadherins, named 'cadherin switch', concerning the down-regulation of E-cadherin expression mediating strong adhesion signal, and recognized as an invasion suppressor, and the up-regulation of N-cadherin expression inducing more motile and invasive phenotype of cells have been suggested either during development or in cancer, where it may be concomitant with cancer progression steps [37–39]. The 'cadherin switch' has been observed and described as an indispensable step, enabling the epithelial-to-mesenchymal transition (EMT).

2.2. Role of cadherins in epithelial-to-mesenchymal transition

EMT is a process of dedifferentiation, which has been described by three major cell phenotype changes, including (1) diminution of cellular adhesion, as an effect of changes in the expression of adhesion receptors and cytoskeletal proteins; (2) loss of epithelial cell polarity accompanied by morphological changes leading from the cobblestone-like epithelial cells to

spindle-shaped mesenchymal cells; and (3) the acquisition of more motile and invasive behaviour [40, 41]. This process takes place during normal embryonic development as a basic step of tissue remodelling, such as mesoderm formation and neural crest development. It should be noted that the reverse process, named mesenchymal-to-epithelial transition (MET), also occurs evidencing the enormous plasticity of developmental processes [40]. EMT-like processes are observed also in the course of wound healing, during which in response to injury keratinocytes go through a 'metastable' phenotype by losing their contact and therefore move [42]. EMT has been suggested in numerous cancer types, including melanoma and supposed as a conducive to metastasis formation.

2.2.1. EMT molecular markers

Besides or as a consequence of EMT-related 'cadherin switch', more abundant expression of vimentin with simultaneous β-catenin translocation to the nucleus, and increased expression of transcription factors such as Slug, Snail, Twist, EF1/ZEB1, SIP1/ZEB2 and E47 have been observed. They are reported as markers of developmental processes [43–45] and skin cancer cells transformation [38, 46, 47]. It is noteworthy that the suggestion is made on the basis of metastatic BCC observations that the enhanced Twist1 expression may serve as a biomarker of BCC progression [48]. Immunohistochemical analysis of tissue sections of non-metastasizing, metastasizing and lymph node metastasis of cutaneous SCC (cSCC) has revealed that their metastatic potential is accompanied by EMT-marker expression, including the Twist overexpression, while in metastases the expression of selected EMT-related markers has been decreased [49]. Also, the increased expression of other EMT-related markers such as Ki-67 and keratin 17, together with the reduced expression of both E-cadherin and involucrin (early marker of epidermis keratinocytes differentiation), has been shown in the cSCC compared to normal skin biopsies [50].

Some studies suggested that the EMT is closely related with the cancer stem cells (CSCs) biology, and therefore the analysis of expression of CD44 and CD29 (β1-integrin subunit) recognized as CSCs markers has been conducted in cSCC A341 cells. High expression of both markers has been described in cells located in the periphery of cSCC tumours. Simultaneously, a higher N-cadherin and a lower E-cadherin expression have been detected in CD44+/CD29+ cells, legitimizing their EMT [51]. In human, BCC analysis of paraffin-embedded tissue sections suggested strong correlation between tumour progression and the expression of integrin-linked kinase (ILK), which has been proposed there as an EMT marker [52].

The expression of EMT markers has been analysed in desmoplastic melanoma (DM) tumours, which makes diagnostic difficulties because of its unusual clinical appearance. These are mainly amelanotic, deep cutaneous tumours surrounded by sun-damaged skin [53]. The comparison of EMT markers expression profile conducted in tissue microarrays of DM and primary vertical growth phase non-desmoplastic melanomas (NDMs) has demonstrated a significantly higher expression of EMT-related proteins—N-cadherin, SPARC and WT-1, and the decreased expression of E-cadherin in DM compared to NDM, suggesting usefulness of these markers in DM diagnostics [54].

Another known marker of EMT and tumour metastasis is the elevated expression of N-acetylglucosaminyltransferase V (GnT-V) responsible for β1,6-branching of N-linked complex-type oligosaccharides. In cutaneous wound healing of GnT-V transgenic mice, GnT-V-overexpressed keratinocytes showed spindle-shaped morphology and enhanced migration, which were associated with the early phase of malignant transformation: changes in E-cadherin glycosylation and localization as well as induction of EMT. As a result, EMT-associated factors Snail and Twist were up-regulated, and cadherin switch was observed [55].

2.2.2. EMT-initiating factors

EMT initiation has been attributed to a variety of growth factors, including members of the epidermal growth factor (EGF), the fibroblast growth factor (FGF) and the insulin-like growth factor (IGF) families, hepatocyte growth factor (HGF) and transforming growth factor-β (TGF-β). The intracellular-signalling pathways, induced by these growth factors, have led to characteristic transformation from epithelial, differentiated and proliferative phenotype to mesenchymal, dedifferentiated ready to migration and invasion phenotype. Down-regulated dermal fibroblast secretion of HGF caused by knockdown of RaIA GTPase expression (known contributor in Ras-induced tumourigenesis) has resulted in the suppression of SCC tumour progression. As an effect, the reduced migratory abilities of neighbouring keratinocytes, related to the changes in expression levels of E-cadherin (increased) and transcription factors —Snail and Slug—suppressing E-cadherin RNA level, have been observed [56]. The TGF-β-induced EMT has been observed in melanoma cells and accompanied by the activation of the PI3K and platelet-derived growth factor (PDGF)-signalling pathways triggering the up-regulation of N-cadherin expression and the transformation of a proliferative phenotype of cells into a more invasive one [57].

The involvement of PI3K/AKT-signalling pathway has also been suggested in EMT of SCC cells. The analysis of isogenic cell lines derived from succeeding stages of keratinocytes malignant transformation, that is, dysplastic forehead skin (PM1), primary cSCC (MET1) and its lymph node metastasis (MET4), has shown the correlation between tumour progression and the activation of AKT. Additionally, it has been reported that the inhibition of AKT activity results in the decreased cell migration and invasion, reduced cell detachment and reduced expression of EMT markers such as Slug and vimentin concomitantly with the up-regulation of E-cadherin expression [46].

There are also some data concerning the relevance of cytokine IL-6 secretion during the inflammatory processes for the initiation of EMT and subsequent malignant transformation of normal human keratinocytes of HaCat cell line. In response to arsenite treatment, the elevated IL-6 secretion has been observed leading to the increased level of miR-21, microRNA related with the malignancies and overexpressed in most cancers. The arsenite-transformed HaCat cells have shown the changed expression level of E-cadherin (decreased) and vimentin (increased), which was linked with the initiation of EMT process and increased migration capacity of transformed cells [58]. As melanoma patients are characterized by a higher IL-6 serum level, its important role in the stimulation of melanoma progression has been suggested.

In a mouse melanoma model, the action of IL-6 has led to the increased metastatic potential due to up-regulation of Twist expression and subsequent N-cadherin overexpression. Thus, therapies directed specifically against IL-6 could possibly reduce the tumour progression [59].

In response to mechanical tissue damage, and succeeding action of cytokines and growth factors (TGF-β, EGF), the activation of specific signalling pathways has been reported in skin keratinocytes, leading to the activation of Snail—a regulator of keratinocytes inflammatory response and an EMT marker. Snail protein acts as gene transcription repressors, and E-cadherin gene has been recognized as its prototypic target. Down-regulated E-cadherin expression facilitates the process of wound healing by losing adhesion between keratinocytes, EMT promotion and subsequent keratinocyte migration. Likewise, in the course of keratinocyte neoplastic transformation, signalling via Snail promotes migration and invasion phenotype, proinflammatory microenvironment and degradation of extracellular matrix characteristic for SCC [60]. These processes are similar in many carcinoma types and suggestion has been made that tumours resemble wounds that do not heal [61].

2.3. Cancer-related changes in cadherin expression

While the neoplastic transformation of many cell types is accompanied by the loss of or disturbances in gap junction formation, the neoplastic transformation of melanocytes and keratinocytes follows the same path. It has been observed that the diminished E-cadherin expression level, typical for melanoma cells, disturbs their interaction with adjacent keratinocytes and therefore prevents the regulating influence of keratinocytes on the melanoma cells growth and differentiation [62]. The large body of evidence has suggested that melanoma cells transformation from non-malignant to invasive ones is accompanied by the loss of E-cadherin and overexpression of N-cadherin. It has been suggested, however, that not N-cadherin itself had been responsible for the start of melanoma cells dissemination and metastasis formation [63]. Observations have revealed that the deregulation of E- and N-cadherin expression is involved in tumourigenesis and cancer progression also in other skin cancers—MCC, SCC and BCC [52, 58, 64, 65].

2.3.1. E-cadherin

The important role of E-cadherin expression for the malignant transformation of melanoma cells and SCC has been confirmed in numerous tissue samples assembled in tissue microarrays of human malignant melanoma and SCC as well as in selected cell lines, including A375, SK-MEL-24, MV3 and M14 melanoma cell lines. As a conclusion of this analysis, Tang et al. [66] have postulated the reverse correlation between the E-cadherin expression level and the expression of ubiquitin protein ligase E3C (UBE3C), which positively regulates tumour growth and metastasis by inducing the mesenchymal phenotype of melanoma cells. In melanoma, E-cadherin expression has been also shown to be correlated with the altered expression of microRNA (miRNA). Analysis of frozen melanoma tissue section demonstrated that the decreased expression of mi-R200a, mi-R200c, and miR-203, previously described as contributors of melanoma metastasis, correlated with down-regulation of E-cadherin and growing

http://dx.doi.org/10.5772/64666

tumour thickness. These data reveal miRNA role in the regulation of E-cadherin expression in the course of melanoma progression [67].

α-catulin is a cytoplasmic molecule, overexpressed in melanoma that has been recognized as a negative regulator of E-cadherin expression, consequently promoting melanoma progression. It has been confirmed in α-catulin knockdown experiments, where the enhanced melanoma cells binding to keratinocytes as well as up-regulated E-cadherin expression have been observed resulting in the lower migratory and invasive potential of melanoma cells [68].

In BCC, it has been observed that tumour progression is accompanied by the decreased membranous expression of E-cadherin. Additionally, the increased nuclear localization of E-cadherin, as well as nuclear translocation of β-catenin, has been shown [52].

Analysis of 227 tissue sections of MCC has revealed weak and mainly cytoplasmic staining for E-cadherin and there were no statistically significant differences in the immunoreactivity between various tumour locations (primary, local or distant metastasis), suggesting that E-cadherin is not relevant for MCC progression [69].

The loss of E-cadherin has been suggested to be a trigger of cancer progression especially because of the reduced cell-cell adhesion and possible stimulation of T cell factor (TCF)-regulated genes, responsible for proliferation and invasion (c-myc, cyclin D1, fibronectin and matrilysin), as an effect of released β-catenin migration to nucleus [19]. The expression of E-cadherin is regulated by different transcription factors including grainyhead-like 3 (Grl-3) factor, which has been shown to participate in the regulation of differentiation and migration of epithelial cells during embryonic development. In normal human keratinocytes (HaCat) and human SCC (A431) cells, the reverse correlation between Grl-3 and E-cadherin expression level has been shown and the induced overexpression of Grl-3 in A431 cells has led to the increased motility and invasion of cancer cells as an effect of E-cadherin down-regulation [65].

Another transcription factor, regulating E-cadherin expression, is Slug. Its presence has been confirmed in multiple melanoma tissue sections, and higher expression has been attributed to nevi than to primary or metastatic melanoma. Such observations have suggested that higher Slug expression is required at the beginning of melanocyte neoplastic transformation but not during melanoma progression. However, in melanocytes and melanoma cells cultured *in vitro*, the exogenous expression of Slug has resulted in the down-regulated expression of E-cadherin and up-regulated expression of N-cadherin and subsequently more efficient cellular migration and invasion [70].

E-cadherin regulatory potential has been attributed also to NOTCH receptors and their signalling pathways. In a set of tissue samples from skin cancer and their adjacent normal skin, the analysis of NOTCH expression has shown the up-regulated receptor expression along with increased Snail and decreased E-cadherin expression in cancer tissue. Simultaneously, the up-regulation/inhibition of NOTCH signalling in A341 cells has resulted in changes in E-cadherin expression, decrease or increase, respectively. The observed effects of NOTCH alteration in SCC have been mediated by Snail up-regulation and subsequent E-cadherin promoter methylation [71].

The experiments with induced E-cadherin suppression in Ras-transformed keratinocytes have revealed the importance of E-cadherin role in SCC neoplastic transformation. E-cadherin absence has increased Src activity leading to the up-regulated expression of FAK that supported the progression of tumour malignancy also by the following deregulation of E-cadherin-dependent adhesion [72].

In melanoma, cadherin switch has been widely described but its molecular mechanism is still not fully explained. To deal with this, Hao et al. [73] using a set of melanoma cell lines from different stages of progression have analysed the expression profile of E- and N-cadherin, PI3K/PTEN pathway components and Snail, Slug and Twist transcription factors. They have shown the correlation between the loss of PTEN activity and E- to N-cadherin switch. The observed cadherin changes have been regulated at the transcriptional level by Twist and Snail, which activity in PTEN-null cells was stimulated by constitutively active PI3K. It has also been reported that the membranous localization of E-cadherin is not controlled by PI3K/PTEN but more likely depends on cadherin-β-catenin interaction [73]. The study on a vast range of primary melanoma tissue samples has confirmed the correlation between down-regulated PTEN expression and 'cadherin switch'. Additionally, this study has shown the linkage of these markers with melanoma progression parameter, that is, Breslow thickness of primary tumours, ulceration and tumour stage. The immunohistochemical detection of E- and N-cadherin as well as PTEN has been conducted and the statistical analysis of results has shown that E-cadherin, unlike N-cadherin, possesses a predictor value. Low E-cadherin expression level has been correlated with a better survival prognosis, without relapses and distant metastasis [74].

Cadherin-mediated adhesion is regarded as a dynamic process adapting to the epithelial tissue remodelling during development and wound healing but also during carcinogenesis. Considering this fact, the proteolytic cleavage of E-cadherin has been suggested as a mechanism of rapid adhesion changes. The role in E-cadherin shedding has been attributed to different ADAMs (a disintegrin-like and metalloproteinase) and MMPs (matrix metalloproteinases) [75]. As a result of its action, a decreased membranous E-cadherin expression and an increased level of 80-kDa soluble E-cadherin fragment (sE-cadherin) in tumour microenvironment have been reported in human SCC clinical tissue samples and SCC mouse model. Moreover, sE-cadherin binding with HER/IGF-1R has been observed, and the consequent initiation of pro-oncogenic signalling, resulting in cancer cell migration, proliferation and invasion, has been reported. Thus, the sE-cadherin has been suggested as a potential therapeutic target in skin cancer treatment [76]. The potential therapeutic value of anti-sE-cadherin antibody has been suggested in SCC model PAM212 cell line. This antibody has inhibited tumour growth, enhanced cell death and silenced the pro-survival pathways by the inhibition of proto-oncogenes (RTKs, IAPs and MDM2) and stimulation of tumour suppressor genes (PTEN and p53) [77].

The diagnostic usefulness of E-cadherin expression changes has been determined for melanoma versus Spitz tumours distinction (Spitz tumour; a benign cutaneous melanocytic tumour). Such distinction is often problematic because of poor reproducibility of Spitz tumour features and therefore unequivocally delineated diagnostic criteria. The obtained results have

http://dx.doi.org/10.5772/64666

suggested that the quantitative differences rather than qualitative irregularities in E-cadherin immunoreactivity could have diagnostic potential [78].

Studies in a variety of melanoma cell lines have shown that the restoration of E-cadherin expression leads to the renewing of communication with keratinocytes and inhibition of melanoma cells invasion [79]. E-cadherin-restored expression has also been observed in SCC cells treated with flavonoids. Highly invasive A431-III cells selected from the parental A341 cell line have been analysed. The invasive potential of A341-III cells has been attributed to their mesenchymal-like phenotype resulting from 'cadherin switch'. Cells have been treated with plant flavonoids: luteolin and quercetin. They are known for their anticancer activity resulting in the inhibition of cell growth, induction of apoptosis and differentiation, as well as the diminution of tumour angiogenesis, cancer cells adhesion, invasion and metastasis. As an effect, A341-III cells have remodelled their morphology to more epithelial-like. It was accompanied by changes in the EMT markers expression level, including down-regulation of N-cadherin and up-regulation of E-cadherin, leading to the renovation of the cell-cell junctions. Therefore, both flavonoids used have been suggested to have chemopreventive, anticancerogenic or chemotherapeutic activity, mainly through their EMT-reverting potential [80].

2.3.2. P-cadherin

The role of P-cadherin in carcinogenesis is ambiguous. It has been shown to promote the invasive behaviour of cancer cells; however, in melanoma it has been reported as a tumour growth suppressor [81]. Clinical data have shown that in general, melanocytic cells in compound nevi and melanomas express E- and P-cadherins; however, a reduction in the expression thereof has been observed in correlation to the depth of melanoma cells dermal localization. It has been suggested that this loss represents melanoma cells' adaptation to the changed microenvironment of the dermis and makes them less dependent on microenvironmental stimulation leading to the increased cell proliferation and melanoma progression [82]. Additionally, the potential usefulness of P-cadherin as a prognostic marker for immunohistochemical detection and diagnosis in patients with primary melanoma of less than 2-mm tumour thickness has been suggested [83]. In melanoma, the alteration of P-cadherin expression in a tissue section of different stages has been shown together with its switch from membranous to cytoplasmic localization. These changes have strongly correlated with patient's survival prognosis, suggesting P-cadherin as a useful marker of melanoma progression [84].

2.3.3. N-cadherin

The analysis of E-, N- and P-cadherin expression has been conducted in human MCCs and in Merkel cells of the healthy epidermis. It has shown the high level of N-cadherin expression in all MCCs with a simultaneous lack of immunoreactivity in the healthy epidermis. The strong E- and P-cadherin positive reaction of Merkel cells and only partial positive immunoreaction for both cadherins in MCCs have also been shown. These results have suggested that 'cadherin switch' takes place also during Merkel cells neoplastic transformation. Additionally, the loss of P-cadherin expression in MCCs has been linked with a more advanced clinical stages, while

its expression has been significantly more frequent in primary MCC [64]. The study of Vlahova and co-workers has shown the similarity in P-cadherin immunoreactivity between primary tumours and distance metastasis of MCCs, while the lymph node metastases have exhibited a lower level of P-cadherin expression. Additionally, the analysis suggested that the membranous expression of P-cadherin in MCCs positively correlates with a prolonged survival prognosis [85]. Depending on the expressed cadherin type, melanoma cells, compared to melanocytes, have been shown to possess different preferences in cell-cell communication. Melanocytes interact mostly with their neighbouring keratinocytes, while melanoma cells preferentially form their gap junction with fibroblasts and among themselves. It has also been observed that gap junction could be established between melanoma cells and N-cadherin expressing endothelial cells, suggesting that the gap junction formation is rather dependent on N-cadherin expression than cell-type-specific [79]. N-cadherin-dependent heterotypic cell-cell adhesion has been described between fibroblasts and WM1205Lu melanoma cells with Smad7 overexpression. In this model, cells have been arrested in their invasion abilities. It has been suggested that the subsequent loss of N-cadherin expression during the following steps of melanoma progression may be a key factor for metastasis formation, because melanoma cells by losing their interaction with fibroblasts become able to migrate to distant metastatic sites, and after that N-cadherin expression can be restored [86]. Additionally, the role of N-cadherin expression for primary (WM793, WM115) and malignant melanoma cells (WM1205Lu, WM266-4 cell lines) proliferation has been analysed with the use of specific N-cadherin siRNA. The observed decrease in N-cadherin expression level up-regulates the cell cycle inhibitors p15, p16, p21 and p27 expression leading to cell cycle arrest in G1 phase and significantly down-regulates AKT, ERK and β-catenin signalling, resulting in the inhibition of cell proliferation [87].

2.3.4. T-cadherin

During malignant transformation of melanocytes, the expression of T-cadherin on both mRNA and protein levels decreases, mainly due to the repression of CDH13 promoter activity by BRN2 transcription factor [36], and finally disappears in human malignant melanomas [88]. Down-regulation of T-cadherin expression is accompanied by a higher growth, proliferation, migration and invasion of malignant cells *in vitro*. Re-expression of T-cadherin in human melanoma cells, via stable transfection, draws back these effects *in vitro* and in a xenograft mouse model *in vivo* [89]. Re-expression of T-cadherin also elevates the apoptotic rate of melanoma cells *in vitro* through down-regulation of AKT and FoxO3a, which is in turn accompanied by the down-regulation of anti-apoptotic molecules BCL-2, BCL-x and clustering from one site and deactivation of transcription factors CREB and AP-1 from another site [90]. Furthermore, ectopic up-regulated T-cadherin sensitizes the apoptosis induced by treatment with CD95/Fas antibody CH-11 [90]. Contradictory results have been demonstrated for a fully mouse model of melanoma, where up-regulated T-cadherin acted oppositely at the same time: as a positive and a negative regulator of mouse melanoma development [91]. Namely, it has been shown that the overexpression of T-cadherin in B16F10 mouse melanoma promotes primary tumour growth due to the recruitment of mesenchymal stromal cells, as well as enhances cell motility, invasiveness and metastasis formation in BDF1 mice in parallel with the

inhibition of neovascularization of primary melanoma sites [91]. This apparent discrepancy has been explained by the recent study, which showed that in the species-specific environment T-cadherin-overexpressed melanoma cells up-regulated the level of pro-oncogenic integrins, chemokines, adhesion molecules and extracellular matrix components, which in turn increased the invasive potential of tumour cells [92]. It is believed that T-cadherin is an endogenous suppressor of keratinocyte proliferation by delaying the G2/M phase progression [93]. It has been shown that T-cadherin is also a suppressor of keratinocyte migration and invasion, and the inactivation of T-cadherin, through allelic loss or hypermethylation of a gene-promoter region, may induce keratinocyte-derived aggressive epithelial tumours with high metastatic potential [94]. Inverse correlations between T-cadherin expression and pre-cancerous (AK, BD), benign (KA) and malignant skin diseases (invasive SCC and BCC) have been well documented in immunohistochemical and *in vitro* studies [88, 95–98]. In other works, the expression of T-cadherin was found to be higher in superficial, nodular or infiltrative BCCs [99] as well as in differentiated/primary SCCs [100] than in normal keratinocytes; however, it was mainly restricted to the leading fronts of the tumours, where the up-regulated T-cadherin induced a morphological spread and inhibited cell invasive potential [100]. It has been shown that ectopic up-regulation of T-cadherin increased SCC cell-matrix adhesiveness by promoting the retention of both β1 integrin and epidermal growth factor receptor (EGFR) in lipid raft domains, and by increasing integrin β1-activation in parallel with the suppression of tyrosine phosphorylation of EGFR [101, 102].

The molecular mechanisms underlying T-cadherin function as a guardian maintaining a non-invasive phenotype of keratinocytes are different from those typically associated with EMT and consist in the indirect negative regulation of EGFR pathway activity; gain or loss of T-cadherin expression switches EGFR signalling off or on, respectively. On the other hand, loss of T-cadherin in SCC may lead to ligand-dependent EGFR hyperactivation and acquiring invasive and aggressive phenotype [102]. It has been shown that co-culture of SCC cells with epithelial cells stimulated ECs to produce EGF [103], which in turn facilitated transendothelial migration of T-cadherin-silenced cells, and their growth within the invaded stroma [104]. In human A431 cells (SCC), EGF-induced phosphorylation of EGFR and resulting downstream signalling through p38MAPK, Erk1/2 and Rac1 contributed to the re-localization of T-cadherin within the plasma membrane from dispersed to focused in intercellular junctions, where it indirectly co-localizes with activated EGFR. Being in complex with p-EGFR, T-cadherin acts as an attenuator for EGFR signalling and its loss shifts the balance between Erk1/2-p38MAPK in favour of Erk1/2 activity [104]. In this way, plasma membrane-associated T-cadherin functions as a regulatory factor, which promotes or represses EGF effects mediated by MAP kinases.

2.3.5. Proteins interacting with cadherins

Cadherins as adhesion receptors are players in the interdependent adhesion network and it is still an issue to decipher the mechanism of their direct interaction with other adhesion proteins. Studies show that E- and N-cadherins participate in the adhesion along with integrins and their interaction with $\alpha_2\beta_1$-integrin has been examined in melanoma cell line and tissue

microarray and tissue section. Simultaneous expression of E- and N-cadherins with $\alpha_2\beta_1$-integrin has been reported in numerous primary and metastatic melanoma cells, and the differentiated localization of such complexes has been observed suggesting their independency. It has also been suggested that $\alpha_2\beta_1$-integrin/N-cadherin complex interplays in the regulation of melanoma cells invasion and migration, while the $\alpha_2\beta_1$-integrin/E-cadherin complex affects cell-cell adhesion [105].

Another receptor cross-talking with E-cadherin is EGFR, which overexpression has been commonly reported in many types of cancer, including skin cancer, and this interaction is of particular interest regarding tumour progression. The association between both receptors is realized via domain of β-catenin, which has been shown to participate in ligand-induced E-cadherin signalling resulting in the inhibition of EGF-dependent cell growth. It has been suggested that homophilic binding of E-cadherin interrupts the activation-signalling pathway subsequent to EGFR without blocking receptor activation [106]. On the other hand, activated EGFR has been described as an upstream regulator of Twist expression leading to its overexpression and alternating E-cadherin down-regulation together with EMT of SCC cells. These observations have suggested mutual regulation between E-cadherin and EGFR [107]. Additionally, the analysis of head and neck SCC has revealed that E-cadherin loss is accompanied by the transcriptional up-regulation of EGFR and results in the increased cell proliferation due to enhanced EGFR signalling [108]. EGFR has also been reported to regulate E-cadherin-dependent cell-cell adhesion by the modulation of E-cadherin assembly with actin cytoskeleton and vinculin, and EGFR activation has led to the distraction of cadherin-vinculin-actin complexes [109].

Interesting interaction has also been described between E-cadherin and caveolin-1, which is generally recognized as a tumour suppressor; however, its contribution to metastasis formation has also been described. In melanoma cells, the co-expression and observed co-localization of E-cadherin and caveolin-1 have resulted in the decreased cell proliferation, enhanced cell death and reduced subcutaneous tumour growth. Despite the reduced E-cadherin expression, related with 'cadherin switch' occurring in melanoma progression, caveolin-1 expression has increased in the analysed metastatic melanomas and correlated with higher tumour malignancy. Due to collectively observed N-cadherin expression, their potential cooperation with caveolin-1 in lung metastasis formation has been suggested [110].

3. Alterations in glycophenotype of cells in skin cancers

Nowadays, instead of the conventional histopathological diagnosis, the antibody or lectin histochemistry approaches are used to distinguish between normal, pre-neoplastic, benign and malignant skin tissues and to improve a quantitative assessment of cancer progression [111]. For example, AK, KA, SCC and BCC show lower expression of high mannose-type and/or hybrid-type N-glycans as well as fucose α1,2-linked to galactose residue (H antigen) compared to normal tissue. However, cutaneous tumours (SCC, BCC, invasive melanoma) display higher expression of truncated mucin-type O-glycan, that is, T antigen (Galβ1-3Gal-

http://dx.doi.org/10.5772/64666

NAc residue) than normal tissue [111–113]. Mannose-type and/or hybrid-type N-glycans and T antigen can be used as markers for the distinction between BCC and TE [111]. Higher-expression levels of β-galactoside α-2,3 sialyltransferase (ST3Gal I) and higher cell-surface reactivity with *Maackia amurensis* agglutinin (MAA), which recognizes sialic acid α2,3-linked to Gal residue, allow to distinguish AK and SCC from KA, BCC and normal epidermis [113, 114]. MCCs do not show expression of neither α2,3-linked sialic acid nor H antigen [115]. By contrast, the expression of β-galactoside α-2,6-sialyltransferase (ST6Gal I) is higher in skin tumours with a greater potential for invasion and metastasis, as in the case of SCC, BCC and melanoma [114, 116]. The difference in the expression level of α2,6-linked sialic acid distinguishes premalignant AK stage from the invasive SCC stage of skin cancer. Unlike the normal and non-malignant epidermis, pre-malignant biopsies and malignant cells from patients with BCC and SCC are positive with the sialylated Le^a structure [117]. Additional O-acetylation at C-9 of sialic acid residue is prominent in melanoma and BCC [116]. It has been shown that very intense binding of mistletoe lectin I (ML-I; which is specific for galactose and Neu5Acα2-6Galβ-) and of *Helix pomatia* agglutinin (HPA; it selectively binds to T and Tn antigens) was positively correlated with the metastasis of melanoma and were not expressed in benign nevus cells, and thus they are predictors of poor prognosis [118–120].

4. Glycosylation of cadherins the skin cancers

Cadherins, like other adhesion proteins, are strongly glycosylated, as they possessed a number of potential N-glycosylation sites in their extracellular domain and O-glycosylation sites in the cytoplasmic domain. Based on the analysis of amino acid sequence, human E-cadherin possesses four potential N-glycosylation sites in its extracellular domain, located at Asn residues 554, 566, 618 and 633 [28], in EC4 and EC5 [121]. N-cadherin ectodomain has been reported to contain eight potential N-glycosylation sites, but only three of them, located in EC2 and EC3, were effectively N-glycosylated [122].

Despite the described redundancy of possible N-glycosylation sites, it has been shown that up to 20% of total molecular mass of cadherin may come from the N-glycan component, and it is the most prominent cadherin post-translational modification. In a culture, more abundant N-glycosylation of E-cadherin has been observed in sparsely growing cells than in dense ones. E-cadherin from sparse cultures has been shown to possess mainly complex-type and lack the high mannose-type N-glycans. On the contrary, N-glycans of E-cadherin from cells growing in a dense culture have composed mainly of high mannose-type and only small amounts of complex-type N-glycans have been detected. Furthermore, the differences in E-cadherin turnover have been reported in respect to its glycosylation status. In general, the level of E-cadherin expression in a dense culture is lowered. Also, the constitution and stability of AJs have been affected by E-cadherin changed N-glycans structure and quantity. The high level of E-cadherin N-glycosylation in a sparse culture has led to unstable adhesion and it has been correlated with cell proliferation. On the other hand, in a dense culture, E-cadherin decoration with high mannose-type N-glycans has resulted in the formation of stable AJs and stronger adhesion [10].

Aberrations in N-oligosaccharides composition are also commonly attributed to cancer transformation and progression in various types of cancer cells [123]. The biantennary complex-type and high mannose-type oligosaccharides are characteristic for normal cells, while progressive malignant transformation of cancer cells is accompanied by the synthesis of more branched (tri-, tetra- or even pentaantennary) N-glycans of complex-types, elongated with poly-N-acetyllactosamine chains [124].

There are also some data concerning the abundance and diverse structural composition of N-glycans attached to cadherin observed mostly in melanoma among other skin cancers [125–128] and N-glycosylation role in cadherin function has been confirmed [29]. O-glycosylation of cadherins has also been described, and especially concerning E-cadherin, their role in the inhibition of protein trafficking has been suggested [129].

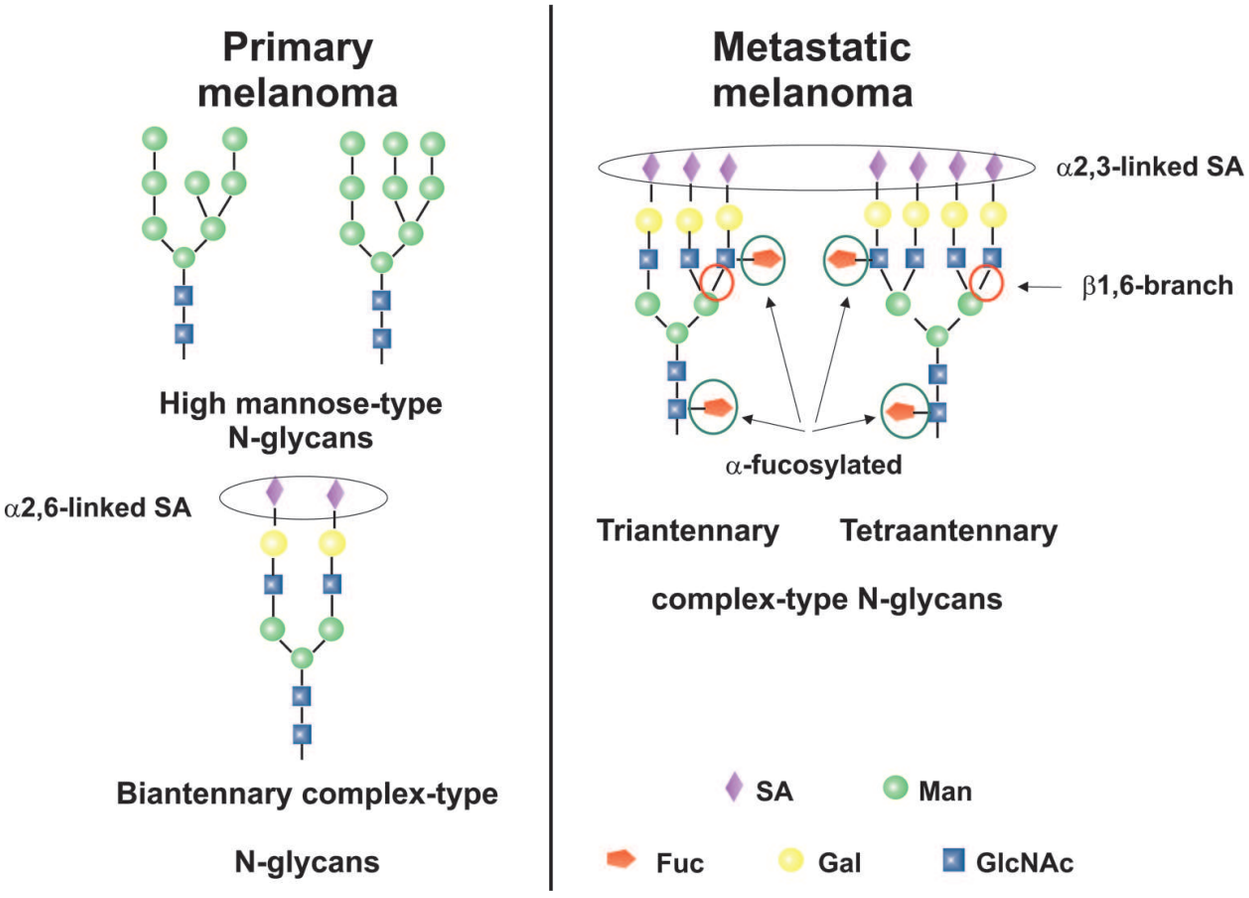


Figure 1. N-glycan structures detected on N-cadherin in melanoma. Gal, galactose; GlcNAc, N-acetylglucosamine; Fuc, fucose; Man, mannose; and SA, sialic acids.

The changed N-glycosylation of cadherins (E- and N-cadherin) has been described in melanoma cells of various cell lines [126–128, 130]. However, this problem has not been studied as extensively as in other types of cancer. The detailed N-glycans analysis showed that N-cadherin

http://dx.doi.org/10.5772/64666

from primary melanoma cells possesses mainly high mannose-type and biantennary complex-type oligosaccharides with α2,6-linked sialic acids, while N-cadherin from metastatic cells possesses mostly tri- and tetraantennary complex-type oligosaccharides, with β1,6-branches, highly α-fucosylated and with α2,3-linked sialic acids (**Figure 1**) [126, 128, 130]. Such observations are in line with observations that more branched N-glycans, especially β1,6-branched oligosaccharides, are associated with a higher motility of tumour cells and its more invasive behaviour. In mouse melanoma model B16F10 cells, E-cadherin was shown to be a target protein for N-acetylglucosaminyltransferase III (GnT-III) action, which is suggested to be a suppressor of the invasive phenotype. In GnT-III-transfected melanoma cells, E-cadherin has been found to bear the bisecting GlcNAc structures which prolonged E-cadherin turnover and resistance to proteolysis. As an effect, the enhancement of cadherin-dependent cellular adhesion leading to the suppression of metastasis has been observed [125].

5. Conclusions

It is commonly accepted that cadherins play a crucial role in cancer progression. Their expression abnormality taking place in different stages of skin cancer progression as well as changes in their glycosylation status leading to adhesion impairment precedes tumour cells dissemination and metastasis formation. The detailed analysis of cadherin-related glycosylation changes in cancer cells could be a key for better understanding of the nature of malignant transformation process and may open new opportunities for the development of more effective anticancer therapeutics and diagnostic tools.

Acknowledgements

Writing of this manuscript was supported in part by grants from the Institute of Zoology, Jagiellonian University in Krakow (K/ZDS/005403) and from the National Science Centre, Poland (2013/11/B/NZ4/04315).

Author details

Marcelina E. Janik*, Dorota Hoja-Łukowicz and Małgorzata Przybyło

*Address all correspondence to: marcelina.janik@uj.edu.pl

Department of Glycoconjugate Biochemistry, Institute of Zoology, Jagiellonian University, Kraków, Poland

References

[1] Bassagañas S, Carvalho S, Dias AM, Pérez-Garay M, Ortiz MR, Figueras J, Reis CA, Pinho SS, Peracaula R. Pancreatic cancer cell glycosylation regulates cell adhesion and invasion through the modulation of α2β1 integrin and E-cadherin function. PLoS One. 2014;9(5):e98595. doi: 10.1371/journal.pone.0098595

[2] Angst BD, Marcozzi C, Magee AI. The cadherin superfamily: diversity in form and function. J Cell Sci. 2001;114(4):629–641.

[3] Dames SA, Bang E, Haüssinger D, Ahrens T, Engel J, Grzesiek S. Insights into the low adhesive capacity of human T-cadherin from the NMR structure of its N-terminal extracellular domain. J Biol Chem. 2008; 283(34):23485–23495.

[4] van Roy F, Berx G. The cell-cell adhesion molecule E-cadherin. Cell Mol Life Sci. 2008;65:3756–3788.

[5] Brooke MA, Nitoiu D, Kelsell DP. Cell–cell connectivity: desmosomes and disease. J Pathol. 2012;226:158–171.

[6] Chen Y-H, Stewart DB, Nelson WJ. Coupling assembly of the E-cadherin/b-catenin complex to efficient endoplasmic reticulum exit and basal–lateral membrane targeting of E-cadherin in polarized MDCK cells. J Cell Biol. 1999;144:687–699.

[7] Niessen CM, Gottardi CJ. Molecular components of the adherens junction. Biochim Biophys Acta. 2008;1778(3):562–571.

[8] Davis MA, Ireton RC, Reynolds AB. A core function for p120-catenin in cadherin turnover. J Cell Biol. 2003;163(3):525–534.

[9] Herzig M, Savarese F, Novatchkova M, Semb H, Christofori G. Tumor progression induced by the loss of E-cadherin in dependent on beta-catenin/Tcf-mediated Wnt signaling. Oncogene. 2007;26(16):2290–2298.

[10] Liwosz A, Lei T, Kukuruzinska MA. N-Glycosylation affects the molecular organization and stability of E-cadherin junctions. J Biol Chem. 2006;281(32): 23138–23149.

[11] Shapiro L, Weis WI. Structure and biochemistry of cadherins and catenins. Cold Spring Harb Perspect Biol. 2009;1(3):a003053. doi: 10.1101/cshperspect.a003053.

[12] Green KJ, Getsios S, Troyanovsky S, Godsel LM. Intercellular junction assembly, dynamics, and homeostasis. Cold Spring Harb Perspect Biol. 2010;2(2):a000125. doi: 10.1101/cshperspect.a000125.

[13] Canel M, Serrels A, Frame MC, Brunton VG. E-cadherin-integrin crosstalk in cancer invasion and metastasis. J Cell Sci. 2013;126(2):393–401. doi: 10.1242/jcs.100115.

[14] Jeanes A, Gottardi CJ, Yap AS. Cadherins and cancer: how does cadherin dysfunction promote tumor progression? Oncogene. 2008;27(55):6920–6929. doi: 10.1038/onc.2008.343.

[15] Gallin WJ, Edelman GM, Cunningham BA. Characterization of L-CAM, a major cell adhesion molecule from embryonic liver cells. Proc Natl Acad Sci USA. 1983;80(4):1038–1042.

[16] Ogou SI, Yoshida-Noro C, Takeichi M. Calcium-dependent cell-cell adhesion molecules common to hepatocytes and teratocarcinoma stem cells. J Cell Biol. 1983;97(3):944–948.

[17] Peyriéras N, Hyafil F, Louvard D, Ploegh HL, Jacob F. Uvomorulin: a nonintegral membrane protein of early mouse embryo. Proc Natl Acad Sci USA. 1983;80(20):6274–6277.

[18] Halbleib JM, Nelson WJ. Cadherins in development: cell adhesion, sorting, and tissue morphogenesis. Genes Dev. 2006;20(23):3199–3214.

[19] Hazan RB, Qiao R, Keren RT, Badano I, Suyama K. Cadherin switch in tumor progression. Ann NY Acad Sci. 2004;1014:155–163. doi: 10.1196/annals.1294.016

[20] Inuzuka H, Redies C, Takeichi M. Differential expression of R- and N-cadherin in neural and mesodermal tissues during early chicken development. Development. 1991;113(3):959–967.

[21] Vestweber D, Winderlich M, Cagna G, Nottebaum AF. Cell adhesion dynamics at endothelial junctions: VE-cadherin as a major player. Trends Cell Biol. 2009;19(1):8–15. doi: 10.1016/j.tcb.2008.10.001.

[22] Prakash S, Swaminathan U. β catenin in health: a review. J Oral Maxillofac Pathol. 2015;19(2):230–238. doi: 10.4103/0973-029X.164537.

[23] van Roy F. Beyond E-cadherin: roles of other cadherin superfamily members in cancer. Nat Rev Cancer. 2014;14(2):121–134. doi: 10.1038/nrc3647.

[24] Samuelov L, Sprecher E, Paus R. The role of P-cadherin in skin biology and skin pathology: lessons from the hair follicle. Cell Tissue Res. 2015;360(3):761–771. doi: 10.1007/s00441-015-2114-y.

[25] Shan WS, Tanaka H, Phillips GR, Arndt K, Yoshida M, Colman DR, Shapiro L. Functional cis-heterodimers of N- and R-cadherins. J Cell Biol. 2000;148(3):579–590.

[26] Zhu B, Chappuis-Flament S, Wong E, Jensen IE, Gumbiner BM, Leckband D. Functional analysis of the structural basis of homophilic cadherin adhesion. Biophys J. 2003;84(6):4033–4042.

[27] Stemmler MP. Cadherins in development and cancer. Mol Biosyst. 2008;4(8):835–850. doi: 10.1039/b719215k.

[28] Zhao H, Sun L, Wang L, Xu Z, Zhou F, Su J, Jin J, Yang Y, Hu Y, Zha X. N-glycosylation at Asn residues 554 and 566 of E-cadherin affects cell cycle progression through

extracellular signal-regulated protein kinase signaling pathway. Acta Biochim Biophys Sin (Shanghai). 2008;40(2):140–148.

[29] Pinho SS, Seruca R, Gärtner F, Yamaguchi Y, Gu J, Taniguchi N, Reis CA. Modulation of E-cadherin function and dysfunction by N-glycosylation. Cell Mol Life Sci. 2011;68(6):1011–1020. doi: 10.1007/s00018-010-0595-0.

[30] Nose A, Takeichi M. A novel cadherin adhesion molecule: Its expression pattern associated with implantation and organogenesis of mouse embryos. J Cell Biol. 1986; 103:2649–2658.

[31] Li L, Fukunaga-Kalabis M, Yu H, Xu X, Kong J, Lee JT, Herlyn M. Human dermal stem cells differentiate into functional epidermal melanocytes. J Cell Sci. 2010;123(Pt 6):853–860. doi: 10.1242/jcs.061598.

[32] Keswell D, Kidson SH, Davids LM. Melanocyte migration is influenced by E-cadherin-dependent adhesion of keratinocytes in both two- and three-dimensional in vitro wound models. Cell Biol Int. 2015;39(2):169–176. doi: 10.1002/cbin.10350.

[33] Perlis C, Herlyn M. Recent advances in melanoma biology. Oncologist. 2004;9(2):182–187.

[34] Jouneau A, Yu YQ, Pasdar M, Larue L. Plasticity of cadherin-catenin expression in the melanocyte lineage. Pigment Cell Res. 2000;13(4):260–272.

[35] Derycke LD, Bracke ME. N-cadherin in the spotlight of cell-cell adhesion, differentiation, embryogenesis, invasion and signalling. Int J Dev Biol. 2004;48(5-6):463–476.

[36] Ellmann L, Joshi MB, Resink TJ, Bosserhoff AK, Kuphal S. BRN2 is a transcriptional repressor of CDH13 (T-cadherin) in melanoma cells. Lab Invest. 2012; 92:1788–1800.

[37] Cavallaro U, Schaffhauser B, Christofori G. Cadherins and the tumour progression: is it all in a switch? Cancer Lett. 2002;176(2):123–128.

[38] Paluncic J, Kovacevic Z, Jansson PJ, Kalinowski D, Merlot AM, Huang ML, Lok HC, Sahni S, Lane DJ, Richardson DR. Roads to melanoma: key pathways and emerging players in melanoma progression and oncogenic signaling. Biochim Biophys Acta. 2016;1863(4):770–784. doi: 10.1016/j.bbamcr.2016.01.025.

[39] Lupia A, Peppicelli S, Witort E, Bianchini F, Carloni V, Pimpinelli N, Urso C, Borgognoni L, Capaccioli S, Calorini L, Lulli M. CD63 tetraspanin is a negative driver of epithelial-to-mesenchymal transition in human melanoma cells. J Invest Dermatol. 2014;134(12): 2947–2956. doi: 10.1038/jid.2014.258.

[40] Yang J, Weinberg RA. Epithelial-mesenchymal transition: at the crossroads of development and tumor metastasis. Dev Cell. 2008;14(6):818–829. doi: 10.1016/j.devcel. 2008.05.009.

[41] Verrill C, Cerundolo L, Mckee C, White M, Kartsonaki C, Fryer E, Morris E, Brewster S, Ratnayaka I, Marsden L, Lilja H, Muschel R, Lu X, Hamdy F, Bryant RJ. Altered

expression of epithelial-to-mesenchymal transition proteins in extraprostatic prostate cancer. Oncotarget. 2016;7(2):1107–1119. doi: 10.18632/oncotarget.6689.

[42] Thiery JP, Acloque H, Huang RY, Nieto MA. Epithelial-mesenchymal transitions in development and disease. Cell. 2009;139(5):871–890. doi: 10.1016/j.cell.2009.11.007.

[43] Honjo M, Tanihara H, Suzuki S, Tanaka T, Honda Y, Takeichi M. Differential expression of cadherin adhesion receptors in neural retina of the postnatal mouse. Invest Ophthalmol Vis Sci. 2000;41(2):546–551.

[44] Carver EA, Jiang R, Lan Y, Oram KF, Gridley T. The mouse snail gene encodes a key regulator of the epithelial-mesenchymal transition. Mol Cell Biol. 2001;21(23):8184–8188.

[45] Xu L, Overbeek PA, Reneker LW. Systematic analysis of E-, N- and P-cadherin expression in mouse eye development. Exp Eye Res. 2002;74(6):753–760.

[46] Barrette K, Van Kelst S, Wouters J, Marasigan V, Fieuws S, Agostinis P, van den Oord J, Garmyn M. Epithelial-mesenchymal transition during invasion of cutaneous squamous cell carcinoma is paralleled by AKT activation. Br J Dermatol. 2014;171(5):1014–1021. doi: 10.1111/bjd.12967.

[47] von Maltzan K, Li Y, Rundhaug JE, Hudson LG, Fischer SM, Kusewitt DF. Role of the Slug transcription factor in chemically-induced skin cancer. J Clin Med. 2006;5(2):21. doi: 10.3390/jcm5020021.

[48] Majima Y, Hirakawa S, Kito Y, Suzuki H, Koide M, Fukamizu H, Tokura Y. Twist1 as a possible biomarker for metastatic basal cell carcinoma. Acta Derm Venereol. 2012;92(6):621–622. doi: 10.2340/00015555-1422.

[49] Toll A, Masferrer E, Hernández-Ruiz ME, Ferrandiz-Pulido C, Yébenes M, Jaka A, Tuneu A, Jucglà A, Gimeno J, Baró T, Casado B, Gandarillas A, Costa I, Mojal S, Peña R, de Herreros AG, García-Patos V, Pujol RM, Hernández-Muñoz I. Epithelial to mesenchymal transition markers are associated with an increased metastatic risk in primary cutaneous squamous cell carcinomas but are attenuated in lymph node metastases. J Dermatol Sci. 2013;72(2):93–102. doi: 10.1016/j.jdermsci.2013.07.001.

[50] Lan YJ, Chen H, Chen JQ, Lei QH, Zheng M, Shao ZR. Immunolocalization of vimentin, keratin 17, Ki-67, involucrin, β-catenin and E-cadherin in cutaneous squamous cell carcinoma. Pathol Oncol Res. 2014;20(2):263–266. doi: 10.1007/s12253-013-9690-5.

[51] Geng S, Guo Y, Wang Q, Li L, Wang J. Cancer stem-like cells enriched with CD29 and CD44 markers exhibit molecular characteristics with epithelial-mesenchymal transition in squamous cell carcinoma. Arch Dermatol Res. 2013;305(1):35–47. doi: 10.1007/s00403-012-1260-2.

[52] Papanikolaou S, Bravou V, Gyftopoulos K, Nakas D, Repanti M, Papadaki H. ILK expression in human basal cell carcinoma correlates with epithelial-mesenchymal

transition markers and tumour invasion. Histopathology. 2010;56(6):799–809. doi: 10.1111/j.1365-2559.2010.03556.x.

[53] Chen LL, Jaimes N, Barker CA, Busam KJ, Marghoob AA. Desmoplastic melanoma: a review. J Am Acad Dermatol. 2013;68(5):825–833. doi: 10.1016/j.jaad.2012.10.041.

[54] Garrido MC, Requena L, Kutzner H, Ortiz P, Pérez-Gómez B, Rodriguez-Peralto JL. Desmoplastic melanoma: expression of epithelial-mesenchymal transition-related proteins. Am J Dermatopathol. 2014;36(3):238–242. doi: 10.1097/DAD.0b013e3182987441.

[55] Terao M, Ishikawa A, Nakahara S, Kimura A, Kato A, Moriwaki K, Kamada Y, Murota H, Taniguchi N, Katayama I, Miyoshi E. Enhanced epithelial-mesenchymal transition-like phenotype in N-acetylglucosaminyltransferase V transgenic mouse skin promotes wound healing. J Biol Chem. 2011;286(32):28303–28311. doi: 10.1074/jbc.M111.220376.

[56] Sowalsky AG, Alt-Holland A, Shamis Y, Garlick JA, Feig LA. RalA function in dermal fibroblasts is required for the progression of squamous cell carcinoma of the skin. Cancer Res. 2011;71(3):758–767. doi: 10.1158/0008-5472.CAN-10-2756.

[57] Schlegel NC, von Planta A, Widmer DS, Dummer R, Christofori G. PI3K signalling is required for a TGFβ-induced epithelial-mesenchymal-like transition (EMT-like) in human melanoma cells. Exp Dermatol. 2015;24(1):22–28. doi: 10.1111/exd.12580.

[58] Lu X, Luo F, Liu Y, Zhang A, Li J, Wang B, Xu W, Shi L, Liu X, Lu L, Liu Q. The IL-6/STAT3 pathway via miR-21 is involved in the neoplastic and metastatic properties of arsenite-transformed human keratinocytes. Toxicol Lett. 2015;237(3):191–199. doi: 10.1016/j.toxlet.2015.06.011.

[59] Na YR, Lee JS, Lee SJ, Seok SH. Interleukin-6-induced Twist and N-cadherin enhance melanoma cell metastasis. Melanoma Res. 2013;23(6):434–443. doi: 10.1097/CMR.0000000000000021.

[60] Sou PW, Delic NC, Halliday GM, Lyons JG. Snail transcription factors in keratinocytes: enough to make your skin crawl. Int J Biochem Cell Biol. 2010;42(12):1940–1944. doi: 10.1016/j.biocel.2010.08.021.

[61] Byun JS, Gardner K. Wounds that will not heal: pervasive cellular reprogramming in cancer. Am J Pathol. 2013;182(4):1055–1064. doi: 10.1016/j.ajpath.2013.01.009.

[62] Li G, Satyamoorthy K, Herlyn M. Dynamics of cell interactions and communications during melanoma development. Crit Rev Oral Biol Med. 2002;13(1):62–70.

[63] Laidler P, Gil D, Pituch-Noworolska A, Ciołczyk D, Ksiazek D, Przybyło M, Lityńska A. Expression of beta1-integrins and N-cadherin in bladder cancer and melanoma cell lines. Acta Biochim Pol. 2000;47(4):1159–1170.

[64] Werling AM, Doerflinger Y, Brandner JM, Fuchs F, Becker JC, Schrama D, Kurzen H, Goerdt S, Peitsch WK. Homo- and heterotypic cell-cell contacts in Merkel cells and

Merkel cell carcinomas: heterogeneity and indications for cadherin switching. Histopathology. 2011;58(2):286–303. doi: 10.1111/j.1365-2559.2011.03748.x.

[65] Zhao P, Guo S, Tu Z, Di L, Zha X, Zhou H, Zhang X. Grhl3 induces human epithelial tumor cell migration and invasion via downregulation of E-cadherin. Acta Biochim Biophys Sin (Shanghai). 2016;48(3):266–274. doi: 10.1093/abbs/gmw001.

[66] Tang L, Yi XM, Chen J, Chen FJ, Lou W, Gao YL, Zhou J, Su LN, Xu X, Lu JQ, Ma J, Yu N, Ding YF. Ubiquitin ligase UBE3C promotes melanoma progression by increasing epithelial-mesenchymal transition in melanoma cells. Oncotarget. 2016;7(13):15738–15746. doi: 10.18632/oncotarget.7393.

[67] van Kempen LC, van den Hurk K, Lazar V, Michiels S, Winnepenninckx V, Stas M, Spatz A, van den Oord JJ. Loss of microRNA-200a and c, and microRNA-203 expression at the invasive front of primary cutaneous melanoma is associated with increased thickness and disease progression. Virchows Arch. 2012;461(4):441–448. doi: 10.1007/s00428-012-1309-9.

[68] Kreiseder B, Orel L, Bujnow C, Buschek S, Pflueger M, Schuett W, Hundsberger H, de Martin R, Wiesner C. α-Catulin downregulates E-cadherin and promotes melanoma progression and invasion. Int J Cancer. 2013;132(3):521–530. doi: 10.1002/ijc.27698.

[69] Knapp CF, Sayegh Z, Schell MJ, Rawal B, Ochoa T, Sondak VK, Messina JL. Expression of CXCR4, E-cadherin, Bcl-2, and survivin in Merkel cell carcinoma: an immunohistochemical study using a tissue microarray. Am J Dermatopathol. 2012;34(6):592–596. doi: 10.1097/DAD.0b013e31823e25d3.

[70] Shirley SH, Greene VR, Duncan LM, Torres Cabala CA, Grimm EA, Kusewitt DF. Slug expression during melanoma progression. Am J Pathol. 2012;180(6):2479–2489. doi: 10.1016/j.ajpath.2012.02.014.

[71] Wang Z, Liu L, Wang M, Shen M, Li J, Liu J, Li C, Xin C, Zhu S, Mei Q, Wang Y. NOTCH1 regulates migration and invasion of skin cancer cells by E-cadherin repression. Mol Cell Biochem. 2012;362(1–2):35–41. doi: 10.1007/s11010-011-1125-6.

[72] Alt-Holland A, Sowalsky AG, Szwec-Levin Y, Shamis Y, Hatch H, Feig LA, Garlick JA. Suppression of E-cadherin function drives the early stages of Ras-induced squamous cell carcinoma through upregulation of FAK and Src. J Invest Dermatol. 2011;131(11):2306–2315. doi: 10.1038/jid.2011.188.

[73] Hao L, Ha JR, Kuzel P, Garcia E, Persad S. Cadherin switch from E- to N-cadherin in melanoma progression is regulated by the PI3K/PTEN pathway through Twist and Snail. Br J Dermatol. 2012;166(6):1184–1197. doi: 10.1111/j.1365-2133.2012.10824.x.

[74] Lade-Keller J, Riber-Hansen R, Guldberg P, Schmidt H, Hamilton-Dutoit SJ, Steiniche T. E- to N-cadherin switch in melanoma is associated with decreased expression of phosphatase and tensin homolog and cancer progression. Br J Dermatol. 2013;169(3):618–628. doi: 10.1111/bjd.12426.

[75] Maretzky T, Reiss K, Ludwig A, Buchholz J, Scholz F, Proksch E, de Strooper B, Hartmann D, Saftig P. ADAM10 mediates E-cadherin shedding and regulates epithelial cell-cell adhesion, migration, and beta-catenin translocation. Proc Natl Acad Sci USA. 2005;102(26):9182–9187.

[76] Brouxhon SM, Kyrkanides S, Teng X, Athar M, Ghazizadeh S, Simon M, O'Banion MK, Ma L. Soluble E-cadherin: a critical oncogene modulating receptor tyrosine kinases, MAPK and PI3K/Akt/mTOR signaling. Oncogene. 2014;33(2):225–235. doi: 10.1038/onc.2012.563.

[77] Brouxhon SM, Kyrkanides S, Raja V, Silberfeld A, Teng X, Trochesset D, Cohen J, Ma L. Ectodomain-specific E-cadherin antibody suppresses skin SCC growth and reduces tumor grade: a multitargeted therapy modulating RTKs and the PTEN-p53-MDM2 axis. Mol Cancer Ther. 2014;13(7):1791–1802. doi: 10.1158/1535-7163.MCT-13-0971.

[78] George E, Polissar NL, Wick M. Immunohistochemical evaluation of p16INK4A, E-cadherin, and cyclin D1 expression in melanoma and Spitz tumors. Am J Clin Pathol. 2010;133(3):370–379. doi: 10.1309/AJCP52YVYCTLUOPI.

[79] Hsu M, Andl T, Li G, Meinkoth JL, Herlyn M. Cadherin repertoire determines partner-specific gap junctional communication during melanoma progression. J Cell Sci. 2000;113(9):1535–1542.

[80] Lin YS, Tsai PH, Kandaswami CC, Cheng CH, Ke FC, Lee PP, Hwang JJ, Lee MT. Effects of dietary flavonoids, luteolin, and quercetin on the reversal of epithelial-mesenchymal transition in A431 epidermal cancer cells. Cancer Sci. 2011;102(10):1829–1839. doi: 10.1111/j.1349-7006.2011.02035.x.

[81] Vieira AF, Paredes J. P-cadherin and the journey to cancer metastasis. Mol Cancer. 2015;14(1):178. doi: 10.1186/s12943-015-0448-4.

[82] Krengel S, Grotelüschen F, Bartsch S, Tronnier M. Cadherin expression pattern in melanocytic tumors more likely depends on the melanocyte environment than on tumor cell progression. J Cutan Pathol. 2004;31(1):1–7.

[83] Bauer R, Wild PJ, Meyer S, Bataille F, Pauer A, Klinkhammer-Schalke M, Hofstaedter F, Bosserhoff AK. Prognostic relevance of P-cadherin expression in melanocytic skin tumours analysed by high-throughput tissue microarrays. J Clin Pathol. 2006;59(7):699–705. doi: 10.1136/jcp.2005.034538.

[84] Bachmann IM, Straume O, Puntervoll HE, Kalvenes MB, Akslen LA. Importance of P-cadherin, beta-catenin, and Wnt5a/frizzled for progression of melanocytic tumors and prognosis in cutaneous melanoma. Clin Cancer Res. 2005;11(24 Pt 1):8606–8614. doi: 10.1158/1078-0432.CCR-05-0011

[85] Vlahova L, Doerflinger Y, Houben R, Becker JC, Schrama D, Weiss C, Goebeler M, Helmbold P, Goerdt S, Peitsch WK. P-cadherin expression in Merkel cell carcinomas is

associated with prolonged recurrence-free survival. Br J Dermatol. 2012;166(5):1043–1052. doi: 10.1111/j.1365-2133.2012.10853.x.

[86] DiVito KA, Trabosh VA, Chen YS, Chen Y, Albanese C, Javelaud D, Mauviel A, Simbulan-Rosenthal CM, Rosenthal DS. Smad7 restricts melanoma invasion by restoring N-cadherin expression and establishing heterotypic cell-cell interactions in vivo. Pigment Cell Melanoma Res. 2010;23(6):795–808. doi: 10.1111/j.1755-148X.2010.00758.x.

[87] Ciołczyk-Wierzbicka D, Gil D, Laidler P. The inhibition of cell proliferation using silencing of N-cadherin gene by siRNA process in human melanoma cell lines. Curr Med Chem. 2012;19(1):145–151.

[88] Zhou S, Matsuyoshi N, Liang SB, Takeuchi T, Ohtsuki Y, Miyachi Y. Expression of T-cadherin in basal keratinocytes of skin. J Invest Dermatol. 2002;118(6):1080–1084. doi: 10.1046/j.1523-1747.2002.01795.x.

[89] Kuphal S, Martyn AC, Pedley J, Crowther LM, Bonazzi VF, Parsons PG, Bosserhoff AK, Hayward NK, Boyle GM. H-cadherin expression reduces invasion of malignant melanoma. Pigment Cell Melanoma Res. 2009;22:296–306. doi: 10.1111/j.1755-148X.2009.00568.x.

[90] Bosserhoff AK, Ellmann L, Quast AS, Eberle J, Boyle GM, Kuphal S. Loss of T-cadherin (CDH-13) regulates AKT signaling and desensitizes cells to apoptosis in melanoma. Mol Carcinog. 2014;53:635–647. doi: 10.1002/mc.22018.

[91] Rubina KA, Yurlova EI, Sysoeva VY, Semina EV, Kalinina NI, Poliakov AA, Mikhaylova IN, Andronova NV, Treshalina HM. T-cadherin stimulates melanoma cell proliferation and mesenchymal stromal cell recruitment, but inhibits angiogenesis in a mouse melanoma model. In: Chai J, editor. Research Directions in Tumor Angiogenesis. Rijeka: InTechOpen; 2013, Chapter 6; p. 143–174. doi: 10.5772/53350

[92] Rubina KA, Surkova EI, Semina EV, Sysoeva VY, Kalinina NI, Poliakov AA, Treshalina HM, Tkachuk VA. T-cadherin expression in melanoma cells stimulates stromal cell recruitment and invasion by regulating the expression of chemokines, integrins and adhesion molecules. Cancers (Basels). 2015;7:1349–1370. doi: 10.3390/cancers7030840.

[93] Mukoyama Y, Zhou S, Miyachi Y, Matsuyoshi N. T-cadherin negatively regulates the proliferation of cutaneous squamous carcinoma cells. J Invest Dermatol. 2005;124:833–838. doi: 10.1111/j.0022-202X.2005.23660.x.

[94] Philippova M, Pfaff D, Kyriakakis E, Buechner SA, Iezzi G, Spagnoli GC,. Schoenenberger AW, Erne P, Resink TJ. T-cadherin loss promotes experimental metastasis of squamous cell carcinoma. Eur J Cancer. 2013;49:2048–2058. doi: 10.1016/j.ejca.2012.12.026.

[95] Zhou S, Matsuyoshi N, Takeuchi T, Ohtsuki Y, Miyachi Y. Reciprocal altered expression of T-cadherin and P-cadherin in psoriasis vulgaris. Br J Dermatol. 2003;149(2):268–273.

[96] Takeuchi T, Liang SB, Matsuyoshi N, Zhou S, Miyachi Y, Sonobe H, Ohtsuki Y. Loss of T-cadherin (CDH13, H-cadherin) expression in cutaneous squamous cell carcinoma. Lab Invest. 2002;82(8):1023–1029.

[97] Takeuchi T, Liang SB, Ohtsuki Y. Downregulation of expression of a novel cadherin molecule, T-cadherin, in basal cell carcinoma of the skin. Mol Carcinog. 2002A;35(4): 173–179. doi: 10.1002/mc.10088.

[98] Rubina K, Sysoeva V, Semina E, Kalinina N, Yurlova E, Khlebnikova A, Molochkov V. Malignant transformation in skin is associated with the loss of T-cadherin expression in human keratinocytes and heterogeneity in T-cadherin expression in tumor vasculature. In: Ran S, editor. Tumor Angiogenesis. Rijeka: InTechOpen; 2012, Chapter 6; p. 135–166. doi: 10.5772/26666

[99] Buechner SA, Philippova M, Erne P, Mathys T, Resink TJ. High T-cadherin expression is a feature of basal cell carcinoma. Br J Dermatol. 2009;161:199–201. doi: 10.1111/j. 1365-2133.2009.09195.x.

[100] Pfaff D, Philippova M, Buechner SA, Maslova K, Mathys T, Erne P, Resink TJ. T-cadherin loss induces an invasive phenotype in human keratinocytes and squamous cell carcinoma (SCC) cells in vitro and is associated with malignant transformation of cutaneous SCC in vivo. Br J Dermatol. 2010;163(2):353–363. doi: 10.1111/j. 1365-2133.2010.09801.x.

[101] Mukoyama Y, Utani A, Matsui S, Zhou S, Miyachi Y, Matsuyoshi N. T-cadherin enhances cell–matrix adhesiveness by regulating β1 integrin trafficking in cutaneous squamous carcinoma cells. Genes Cells. 2007;12:787–796. doi: 10.1111/j. 1365-2443.2007.01092.x.

[102] Kyriakakis E, Maslova K, Philippova M, Pfaff D, Joshi MB, Buechner SA, Erne P, Resink TJ. T-cadherin is an auxiliary negative regulator of EGFR pathway activity in cutaneous squamous cell carcinoma: Impact on cell motility. J Invest. Dermatol. 2012;132:2275–2285. doi: 10.1038/jid.2012.131.

[103] Neiva KG, Zhang Z, Miyazawa M, Warner KA, Karl E, Nör JE. Cross talk initiated by endothelial cells enhances migration and inhibits anoikis of squamous cell carcinoma cells through STAT3/Akt/ERK signaling. Neoplasia 2009;11(6):583–593.

[104] Kyriakakis E, Maslova K, Frachet A, Ferri N, Contini A, Pfaff D, Erne P, Resink TJ, Philippova M. Cross-talk between EGFR and T-cadherin: EGFR activation promotes T-cadherin localization to intercellular contacts. Cell Signall. 2013;25:1044–1053. doi: 10.1016/j.cellsig.2013.02.001.

[105] Siret C, Terciolo C, Dobric A, Habib MC, Germain S, Bonnier R, Lombardo D, Rigot V, André F. Interplay between cadherins and $\alpha 2\beta 1$ integrin differentially regulates melanoma cell invasion. Br J Cancer. 2015;113(10):1445–1453. doi: 10.1038/bjc.2015.358.

[106] Perrais M, Chen X, Perez-Moreno M, Gumbiner BM. E-cadherin homophilic ligation inhibits cell growth and epidermal growth factor receptor signaling independently of

other cell interactions. Mol Biol Cell. 2007;18(6):2013–2025. doi: 10.1091/mbc.E06-04-0348.

[107] Lo HW, Hsu SC, Xia W, Cao X, Shih JY, Wei Y, Abbruzzese JL, Hortobagyi GN, Hung MC. Epidermal growth factor receptor cooperates with signal transducer and activator of transcription 3 to induce epithelial-mesenchymal transition in cancer cells via up-regulation of TWIST gene expression. Cancer Res. 2007;67(19):9066–9076. doi: 10.1158/0008-5472.CAN-07-0575.

[108] Wang D, Su L, Huang D, Zhang H, Shin DM, Chen ZG. Downregulation of E-cadherin enhances proliferation of head and neck cancer through transcriptional regulation of EGFR. Mol Cancer. 2011;10:116. doi: 10.1186/1476-4598-10-116.

[109] Hazan RB, Norton L. The epidermal growth factor receptor modulates the interaction of E-cadherin with the actin cytoskeleton. J Biol Chem. 1998;273(15):9078–9084.

[110] Lobos-González L, Aguilar L, Diaz J, Diaz N, Urra H, Torres VA, Silva V, Fitzpatrick C, Lladser A, Hoek KS, Leyton L, Quest AF. E-cadherin determines Caveolin-1 tumor suppression or metastasis enhancing function in melanoma cells. Pigment Cell Melanoma Res. 2013;26(4):555–570. doi: 10.1111/pcmr.12085.

[111] Melo-Júnior MR, Araújo-Filho JLS, Ramos VJ, Patu M, de Paula Machado MCF, Beltrão EIC, Carvalho Jr LB. Digital image analysis of skin neoplasms evaluated by lectin histochemistry: potential marker to biochemical alterations and tumour differential diagnosis. Bras Patol Med Lab. 2006;42(6):455–460. doi: 10.1590/S1676-24442006000600009.

[112] Doré JF, Berthier-Vergnes O, Zebda N, Bailly M, Thomas L, Bailly C, Cochran AJ. Selective expression of PNA-binding glycoconjugates by invasive human melanomas: a new marker of metastatic potential. Pigment Cell Res. 1994;7(6):461–464.

[113] Lima LRA, Bezerra MF, Almeida SMV, Silva LPBG, Beltrão EIC, Carvalho Júnior LB. Glycophenotype evaluation in cutaneous tumors using lectins labeled with acridinium ester. Disease Markers. 2013;35(3):149–154. doi: 10.1155/2013/787130.

[114] Ferreira SA, Vasconcelos JLA, Cavalcanti LCB, Silva RCWC, Bezerra CL, Rêgo MJBM, Beltrão EIC. Expression patterns of α2,3-sialyltransferase I and α2,6-sialyltransferase I in human cutaneous epithelial lesions. Eur J Histochem. 2013;57:e7:41–45. doi: 10.4081/ejh.2013.e7.

[115] Sames K, Schumacher U, Halata Z, van Damme EJM, Peumans WJ, Asmus B, Moll R, Moll I. Lectin and proteoglycan histochemistry of Merkel cell carcinomas. Exp Dermatol. 2001;10:100–109.

[116] Varki A, Schauer R. Sialic acids. In: Varki A, Cummings RD, Esko JD, Freeze HH, Stanley P, Bertozzi CR, Hart GW, Etzler ME, editors. Essentials of Glycobiology. New York: Cold Spring Harbor Laboratory Press; 2009, Chapter 14.

[117] Nilsson LA, Gisslén H, Lindholm A, Lindholm L, Mobacken H. Identification of basal cell carcinomas by means of monoclonal antibodies C50 and C241. J Dermatol Surg Oncol. 1987;13(1):49–51.

[118] Thies A, Moll I, Berger J, Schumacher U. Lectin binding to cutaneous malignant melanoma: HPA is associated with metastasis formation. Br J Cancer. 2001;84(6):819–823. doi: 10.1054/bjoc.2000.1673.

[119] Thies A, Pfüller U, Schachner M, Horny HP, Molls I, Schumacher U. Binding of mistletoe lectins to cutaneous malignant melanoma: implications for prognosis and therapy. Anticancer Res. 2001;21(4B):2883–2887.

[120] Thies A, Berlin A, Brunner G, Schulze H-J, Moll I, Pfüller U, Wagener C, Schachner M, Altevogt P, Schumacher U. Glycoconjugate profiling of primary melanoma and its sentinel node and distant metastases: implications for diagnosis and pathophysiology of metastases. Can Lett. 2007;248:68–80. doi: 10.1016/j.canlet.2006.05.020.

[121] Carvalho S, Catarino TA, Dias AM, Kato M, Almeida A, Hessling B, Figueiredo J, Gärtner F, Sanches JM, Ruppert T, Miyoshi E, Pierce M, Carneiro F, Kolarich D, Seruca R, Yamaguchi Y, Taniguchi N, Reis CA, Pinho SS. Preventing E-cadherin aberrant N-glycosylation at Asn-554 improves its critical function in gastric cancer. Oncogene. 2016;35(13):1619–1631. doi: 10.1038/onc.2015.225.

[122] Guo HB, Johnson H, Randolph M, Pierce M. Regulation of homotypic cell-cell adhesion by branched N-glycosylation of N-cadherin extracellular EC2 and EC3 domains. J Biol Chem. 2009;284(50):34986–34997. doi: 10.1074/jbc.M109.060806.

[123] Adamczyk B, Tharmalingam T, Rudd PM. Glycans as cancer biomarkers. Biochim Biophys Acta. 2012;1820(9):1347–1353. doi: 10.1016/j.bbagen.2011.12.001.

[124] Janik ME, Lityńska A, Vereecken P. Cell migration—the role of integrin glycosylation. Biochim Biophys Acta. 2010;1800:545–555. doi: 10.1016/j.bbagen.2010.03.013.

[125] Yoshimura M, Ihara Y, Matsuzawa Y, Taniguchi N. Aberrant glycosylation of E-cadherin enhances cell-cell binding to suppress metastasis. J Biol Chem. 1996;271(23): 13811–13815.

[126] Lityńska A, Przybyło M, Pocheć E, Hoja-Łukowicz D, Ciołczyk D, Laidler P, Gil D. Comparison of the lectin-binding pattern in different human melanoma cell lines. Melanoma Res. 2001;11:1–8.

[127] Ciołczyk-Wierzbicka D, Gil D, Hoja-Łukowicz D, Lityńska A, Laidler P. Carbohydrate moieties of N-cadherin from human melanoma cell lines. Acta Biochim Pol. 2002;49(4): 991–998. doi: 024904991.

[128] Przybyło M, Martuszewska D, Pocheć E, Hoja-Łukowicz D, Lityńska A. Identification of proteins bearing beta1-6 branched N-glycans in human melanoma cell lines from different progression stages by tandem mass spectrometry analysis. Biochim Biophys Acta. 2007;1770(9):1427–1435. doi: 10.1016/j.bbagen.2007.05.006.

[129] Zhu W, Leber B, Andrews DW. Cytoplasmic O-glycosylation prevents cell surface transport of E-cadherin during apoptosis. EMBO J. 2001;20:5999–6007. doi: 10.1093/emboj/20.21.5999.

[130] Ciołczyk-Wierzbicka D, Amoresano A, Casbarra A, Hoja-Łukowicz D, Lityńska A, Laidler P. The structure of the oligosaccharides of N-cadherin from human melanoma cell lines. Glycoconj J. 2004;20(7–8):483–492. doi: 10.1023/B:GLYC.0000038294.72088.b0.

IntechOpen

IntechOpen