

THE ROLE OF CADHERIN/CATENIN COMPLEX IN MALIGNANT MELANOMA

N. Bonitsis^{1,2}, A. Batistatou³, S. Karantima¹, K. Charalabopoulos^{1,*}

¹Department of Physiology, Clinical Unit, Ioannina University Medical School, Ioannina, Greece

²Department of Dermatology, Ioannina University Medical School, Ioannina, Greece

³Department of Pathology, Ioannina University Medical School, Ioannina, Greece

In the present review article the role of cadherin/catenin complex in cases of malignant melanoma is discussed in some detail. Cadherins represent the most important superfamily of adhesion molecules with epithelial E-cadherin being the most studied. Its role in normal state as well as in cancer invasion and metastasis and some other pathologies is crucial. E-cadherin expression is altered in malignant melanomas and its downregulation or absence is associated with melanoma invasion and metastasis potential. A shift from E-cadherin expression to neural N-cadherin expression in melanocytes is also detected in malignant melanomas formation. In addition, a discussion regarding the role of placental P-cadherin and vascular endothelial VE-cadherin as well as the recently identified molecule of dysadherin, is attempted in brief.

Key Words: adhesion molecules, cadherins, catenins, dysadherin, melanoma.

The role of cell adhesion mechanisms is of vital significance in very important cell features. Basic processes such as embryogenesis, tissue and organ pattern formation and tissue architecture are some of them. It is believed that changes in cell adhesion molecules are implicated in the loss of control of cell proliferation and neoplasia. The adhesion molecules support and direct the exchange of information between two cells; they are not just molecular glue [1]. Deregulation and loss of control of cell-cell interactions is often associated with the establishment of new interactions and the metastasis process [2, 3]. Various classes of cell-cell adhesion molecules are expressed in various human tissues and in the skin as well [4]. At present, adhesion molecules embrace five categories: cadherins, integrins, immunoglobulin gene superfamily members, selectins and CD44.

Cadherins constitute a large superfamily of adhesion molecules. They are transmembraneous glycoproteins that connect one cell to another through calcium ion-dependent binding [5, 6]. Cadherins are important for the intercellular contacts in solid tissues. They form the transembrane part of the adherent junctions. Among them E- (epithelial), N- (neural), P- (placental) and VE- (vascular endothelial) cadherins are the better studied [7, 8]. These adhesive molecules consist of five extracellular domains and a conserved cytoplasmic region. Intracellularly, cadherins bind to a catenin molecule providing a link to the cytoskeleton [8]. Each member of the cadherins superfamily has a specific binding site allowing binding between cadherins of the same subtype in a homophilic fashion [9]. The complex molecular interactions allow cadherins to take part in intercellular communication. They can

modulate in both normal and malignant tissues all functions and differentiation processes. One of those functions is the determination of the location of the melanocytes in the skin. However, during migration melanocyte precursors do not express E- or P-cadherin [8]. Inactivation of cadherins leads to disruption of the cell-cell adhesion. In contrast, inactivation of other adhesion systems, apart from cadherins, has a little effect on adhesion [10]. Except of the sensitivity of cadherins to act in the absence of calcium ions, cadherin function is also disrupted in carcinomas. In particular, loss of E-cadherin expression in human carcinoma cells is associated with invasiveness and dedifferentiation of carcinoma cells [11].

Catenins, which are undercoated cytoplasmic proteins, represent very important molecules strongly associated with the expression and function of cadherins. Catenins (α -, β - and γ -) are proteins with a specific cytoplasmic domain crucial in cadherin function. They link cadherins to the actin filaments network as well as to other transmembrane and cytoplasmic proteins [1]. The part of the cadherin which links to the actin-cytoskeleton is the cytoplasmic tail of the cadherin. The three members (α -, β -, and γ -catenin) compose the catenin family, with α -catenin playing an important role in adhesion [12]. Furthermore, the p120 molecule is regarded to be a new catenin molecule similar to that of γ -catenin. It has been shown that the expression of α - and γ -catenin is reduced or absent in melanocytic nevi and melanomas [13]. Altered expression of catenins is suggested to be associated with the development of the melanocytic lesions. Heterogenous expression of catenins in the same lesion strongly suggests that catenins may be involved in different adhesion mechanisms. No correlation among the various types of catenins was shown regarding their expression pattern in the same study [13]. It must be mentioned that γ -catenin expression is commonly reduced in melanomas, in contrast to β -catenin which is overexpressed, suggesting a possible indirect role

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*Correspondence: Fax: 003 26510 97850

E-mail: kcharala@cc.uoi.gr

Abbreviations used: E-cadherin – epithelial cadherin;
N-cadherin – neural cadherin; P-cadherin – placental cadherin;
VE-cadherin – vascular endothelial cadherin.

of β -catenin as an oncogene in melanoma cases [13]. In the same study, β -catenin was found to be expressed by all benign and malignant melanocytic lesions [13]. Finally, loss of α -catenin expression was directly associated with melanoma progression [13]. The most important changes in cadherin and catenin expression were observed during the vertical growth phase of melanomas. Loss of membranous P-cadherin and β -catenin expression, minimal membranous E-cadherin expression, as well as loss/minor *de novo* membranous N-cadherin expression, represent alterations commonly found in melanoma progression processes. As a result of these changes mentioned just above, cells lose their adhesive capacity and decline their resistance to tumorigenic process [14].

MELANOMA

One of the fastest rising malignancies in the last years turns to be cutaneous melanoma [15]. Generally melanoma begins with benign nevi and progresses to radical and vertical growth [16, 17]. Between those phases melanocytic nevus with lentiginous melanocytic hyperplasia and aberrant differentiation and/or melanocytic dysplasia may occur. Finally, metastases may occur after the vertical phase growth [18]. This propensity of melanoma to metastasise is the most important characteristic that distinguishes it from other types of cutaneous malignancies. The appearance of melanoma may vary regardless the tumor site. Color may also vary from gray or brown to black, red or even dark blue [5, 19, 20].

Solid tumors are characterized by loss of cellular and morphological features, uncontrolled proliferation, invasiveness and colonization of cancer cells to distant organs. It is believed that at least in part this is due to changes taking place in the microenvironment of normal cells and alterations in intercellular communication between neoplastic and normal cells [21]. Melanocytes are located in the basal layer of the epidermis and they maintain during life a stable-ratio of 1:5 with basal keratinocytes [22]. Melanocytes protect keratinocytes through synthesis and donation of melanin after the effect of ultraviolet light action [10]. In cases of nevis or melanomas this balance is not kept and the transformation disturbs the regulated induction of melanocyte division. In normal state, homeostasis, which determines if a cell remains quiescent, proliferates, differentiates, or undergoes apoptosis, should be maintained [23]. The intercellular adhesion of melanocytes with keratinocytes is achieved by adherent and regulatory junctions via participation of E-cadherin molecules. Cadherins without linkage to the actin cytoskeleton may undergo weaker interactions. These cells are believed to be more prone to cell migration [24].

In normal state, the established adhesion between melanocytes and keratinocytes controls the melanocyte growth and the expression of cell surface receptors. The contacts between keratinocytes and melanocytes are established with the extension of melanocytes' dendrites that contribute to the estab-

lishment of multiple contacts. When control process is lost, then melanoma cells escape and melanoma tumorigenesis is started. A shift in the expression of E-cadherin, P-cadherin and desmoglein mainly to N-cadherin is observed in melanoma cells. As a result the anchorage to the basement membrane is lost and homeostasis mechanisms are dysregulated. The dysregulation of the balance of the epidermal melanin units triggers a continuous proliferation of melanocytes leading, finally, to melanoma development [25, 26]. It has been shown that loss of regulatory dominance by keratinocytes occurs in concert with downregulation of E-cadherin expression in melanomas [27]. Functional E-cadherin in melanoma cells is believed to lead to cell adhesion to keratinocytes, protecting thus from motility, proliferation and invasion [28]. Through the complex process of metastasis, tumor cells undergo drastic changes in cell shape and a reorganization of the actin cytoskeleton is observed [29]. Cells separate from the primary tumor mass and migrate through the extracellular matrix, survive in the vascular system and extravasate into foreign environments forming the metastases sites [30]. In contrast, normal melanocytes appear heterotypic gap junctional intercellular communication with keratinocytes [31]. Loss of adhesion to their original neighbors is one of the first steps, which plays significant role in the invasion of melanoma into adjacent tissues as well as in metastasis sites [10].

E-CADHERIN IN MELANOMAS

E-cadherin is a transmembrane glycoprotein localized in the adherence junctions mediating cell-to-cell adhesion through calcium-dependent homotypic interactions [32]. E-cadherin is the most important molecule in the interactions between melanocytes and keratinocytes. Under normal conditions, E-cadherin is expressed on the cell surface of keratinocytes and melanocytes. If E-cadherin is not expressed, keratinocytes cannot interact with the melanocytes, which now are not regulated by the first [10]. Apart from the cell-to-cell interactive role of E-cadherin, it is regarded that it also suppresses epithelial tumor invasiveness and metastasis [6, 33, 34]. Keratinocyte mediated control, such as coordinated proliferation and downregulation of metastasis, is restored by forced E-cadherin expression in melanoma cells [35]. All epidermal layers in human adult and infant skin, including skin appendages, express on their cell surfaces E-cadherin [1]. E-cadherin distribution on all of the plasma membranes of keratinocytes was detected by ultrastructural studies [36]. E-cadherin expression was absent on dermal surfaces of basal cells [36]. However, dense deposits of E-cadherin in the intercellular spaces of desmosomes were observed [36]. Furthermore, it is revealed by immunohistochemical studies that the normal human epidermal melanocytes express E- and P-cadherin in contrast to melanoma cells [37]. This fact was proved by the use of melanoma cell lines, which did not react with antibodies against human E- and P-cadherin [37]. When E-cadherin is not expressed, melanoma cells

escape from the control through keratinocytes. This downregulation of E-cadherin is associated with gap junction incompatibility to keratinocytes [31].

In general, low levels of E-cadherin may play an important role in tumor progression, as occurs in many carcinomas since cadherin loss is associated with absence of differentiation and a more invasive growth pattern [25, 38]. The suppressed E-cadherin expression in carcinoma cells showed an increased invasive potential in *in vitro* studies and the deep components of occasional melanoma showed substantial reductions in cadherin expression [39, 40]. In cases of malignant melanomas soluble E-cadherin levels in serum were increased.

One possible explanation of the elevated serum E-cadherin levels is that the damaged by invasive tumor cells tissue releases E-cadherin. Another explanation is that this soluble form may be degraded from E-cadherin primarily expressed on tumor cells [41, 42]. Loss of functional E-cadherin let melanocytes to escape from the neighboring keratinocytes. In early melanoma stages may still exist a basement membrane part, which becomes irregular and dysfunctional [43].

Very important role in E-cadherin expression plays the Snail protein. Overexpression of the Snail protein reduces E-cadherin expression and increases the metastatic potential of melanoma cells [44]. Suppression of the Snail protein expression reduces the metastatic potential of melanoma cells [45]. Another factor that can also lead to E-cadherin and P-cadherin downregulation in human epidermal melanocytes, is the exposure to UVB-irradiation [46]. Dysfunction of E-cadherin can be seen as change in cellular localization, associated with high invasiveness and metastasis of the overlying melanoma cells [47]. It has been shown that the expression of membranous E-cadherin remains in large amount during malignant transformation in the radical growth phase of melanoma and metastasis process [14]. Downregulation of E-cadherin and/or its dysfunction is regarded to be one of the earlier steps in the development of metastases in carcinomas, in general. This event may also be one of the first steps in the development of metastases in cutaneous melanomas cases [48]. It is now well known that Snail leads to repression of the cell-cell adhesion molecule of E-cadherin. E-cadherin gene is the first gene, which was described to be targeted by Snail protein. Snail belongs to the Snail superfamily of zinc-finger transcription factors. Snail superfamily is important in morphogenesis as well [49]. In a recently published study it was reported an important correlation between E-cadherin expression and the depth of the primary tumor [50]. E-cadherin expression is observed in cultured melanocytes and nevus cells. E-cadherin is rarely found in early stages of the melanocytic tumor and is lost in invasive and metastatic melanoma cells *in vitro* [51]. Downregulation of E-cadherin may also downregulate genes involved in growth and metastasis possibly by affecting the β -catenin/wnt signaling pathways [52]. It has also

been shown that E-cadherin gene is silenced by at least two distinct mechanisms-methylation and trans-repression by the Snail protein [53]. All metastasizing melanomas and their corresponding lymph node metastases may express membranous E-cadherin [47]. These results contradict the invasion suppressor role described for E-cadherin in carcinoma-derived cell lines *in vitro* [54]. Another significant inverse relation was detected between E-cadherin expression and survival in some types of tumors [38, 55, 56]. Another alternative way to observe the E-cadherin function and its relation to the melanoma development, is that by the re-expression of E-cadherin in E-cadherin deficient melanoma cells. Adenoviral gene transfer was used and surprisingly, E-cadherin transduction inhibited N-cadherin expression in melanoma cells [31]. The same was also proved by the use of full length E-cadherin cDNA, which was transduced by the use of an adenoviral vector to E-cadherin negative melanoma cell lines. The result of E-cadherin restoration was reduction of tumorigenicity and melanoma cells' growth retardation; thus, melanocytic phenotype was closer to normal [35]. In three-dimensional skin reconstructs it was clearly shown that E-cadherin in melanoma cells triggers also apoptosis [35]. In some experiments it was revealed that full length E-cadherin transfection downregulates endogenous N-cadherin expression [57]. Although in general, there is a direct association between decreased levels of E-cadherin expression and tumorigenesis, surprisingly in a study an increase of E-cadherin in a malignant lesion was found [32]. Furthermore, although non statistically significant, in another study, it was reported that E-cadherin expression tended to be preserved in melanoma [58]. In a skin reconstruction model, ectopic adenoviral-mediated E-cadherin expression suppresses invasive capacity. Specifically, inhibits some adhesion receptors such as melanocyte cellular adhesion molecule or $\alpha_v\beta_3$ integrin subunit [35]. It is shown that restoration of E-cadherin expression leads to growth retardation and inhibition of the invasiveness and metastasis in carcinoma cells [59]. Several studies have proposed that E-cadherin can act as a molecule that suppresses the invasive ability [39, 60]. If exogenous E-cadherin cDNA is introduced into epithelioid type cells, a partial tumorigenicity suppression is observed. This suggests that E-cadherin can play an inhibiting role against tumor growth [1]. Another role, which can play E-cadherin in melanocytes apart from its tumor suppressor role, is that of the prevention of naevus' formation, as well as melanomas growth and their metastasis [61].

N-CADHERIN IN MELANOMAS

Melanoma cells lose the capability of expressing E-cadherin, but express N-cadherin at high levels *in vitro* and *in vivo* [25, 62]. During the melanoma development this change of cadherin subtypes gives to melanoma cells the ability of direct interaction with other cells that express N-cadherin. Fibroblasts and vascular endothelial cells are some of them. As a result

tumor cells invasion, migration and tumor-stroma cell adhesion are affected. The described communication between cells expressing N-cadherin is achieved through gap junctions [31]. The role of N-cadherin in melanoma metastasis is also suggested by the fact that N-cadherin promotes migration of melanoma cells over dermal fibroblasts [25]. High levels of N-cadherin expression by the melanoma cells play role in the interactions with the N-cadherin positive fibroblasts and endothelial cells [28]. It is obvious that the upregulation of N-cadherin endows melanoma cells with their new adhesive properties [31]. Apart from adhesive properties, loss of E-cadherin and gain of N-cadherin expression during the melanoma progression provides also new communication properties with N-cadherin-expressing neighboring melanoma cells or dermal fibroblasts [63]. It seems that N-cadherin is the basic cadherin expressed by the melanoblastic cells lines *in vitro*. Very important is the amount of N-cadherin produced, since it is associated with the transformation stage. It has been shown with *in vivo* studies that the pattern of expression of cadherins/catenins is dynamic and associated not only with the stage but also with the location of the cells [61]. It is suggested that the switching of E-cadherin to N-cadherin provides the early tumor with important motility and survival advantages; however, endogenous E-cadherin is not affected by the N-cadherin overexpression [64]. The role of N-cadherin mediated cell-cell adhesion could be characterized as dual. It can be involved in the spreading of endothelial process over transmigrated melanoma cells, but also in the early event of transmigration due to the heterotypic adhesion between endothelial and melanoma cells [29]. Thus, N-cadherin plays a very important role in the first stages of melanoma development by affecting adhesion and communication properties, promoting melanoma cells migration on fibroblasts and by the fact that forced expression of N-cadherin in melanocytes promotes migration in general. In investigated melanoma cells lines, migration can be significantly inhibited when the interaction between N-cadherin expressing cells is blocked [65]. Blocking of N-cadherin synthesis and inhibition of β -catenin signaling pathways, lead to impairment of transendothelial migration of melanoma cells [66].

P-CADHERIN IN MELANOMAS

A relatively few data is known regarding P-cadherin expression in malignant melanomas. P-cadherin is expressed on cells of the basal layers as well as on the outer layers of skin appendage [1]. It is suggested that P-cadherin is involved in the proliferating cell compartment [67]. P-cadherin expression in malignant melanomas is related to tumor proliferation and progression supporting the hypothesis that P-cadherin, as E-cadherin, is involved in invasion or metastasis [1]. The expression of P-cadherin in primary melanocytes is well documented. More specifically, a truncated variant of P-cadherin missing the transmembrane and the cytoplasmic region expressed in melanoma cells

has been found [68]. It is believed, therefore, that the soluble variant of P-cadherin blocks interaction between cells, leading to migration and metastasis of the malignant melanoma [69]. Cytoplasmic expression of P-cadherin is associated with increasing tumor thickness, level of invasion and reduced survival [69]. In cultures with P-cadherin negative cell lines, *de novo* expression of P-cadherin led to promotion of cell-cell contact and aggregation [70].

VE-CADHERIN IN MELANOMAS

Another protein belonging to the cadherin superfamily is the adhesive protein VE-cadherin (vascular endothelial cadherin). VE-cadherin is expressed by endothelial cells promoting cell-cell interactions and plays some role in angiogenesis and vascular permeability [71, 72]. VE-cadherin is essential for both the development and the maintenance of blood vessels [73]. Aggressive human cutaneous and uveal melanoma tumor cells express exclusively VE-cadherin, in contrast to poorly aggressive tumor cells [7]. The expression of VE-cadherin by aggressive melanoma tumors is explained by their ability to mimic endothelial cells and form consequently vasculogenic networks [7]. This is possible under certain conditions, whereas melanoma cells form tubular structures and patterned networks [74]. VE-cadherin disappeared from the endothelial contact underneath the melanoma cell. Migration begins with the small melanoma cells penetrating the VE-cadherin negative regions between endothelial cells [29].

DYSADHERIN IN MELANOMAS

Recently it is reported the existence of a cancer-associated cell membrane glycoprotein named dysadherin, with an anti-adhesive role. The expression of this protein in cutaneous malignant melanoma is associated with tumor aggressiveness and seems to be a marker of poor prognosis [58]. E-cadherin function and expression is downregulated by dysadherin. This was proved by experiments where cells transfected with dysadherin cDNA downregulated E-cadherin, and promoted metastasis to the liver in an animal model [75]. Dysadherin expression also was studied in some malignancies in humans by our research group [76–78]. Of course, further studies are needed to elucidate the role of dysadherin in human cancer cases and particularly, in malignant melanomas.

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РОЛЬ КАДГЕРИН/КАТЕНИНОВОГО КОМПЛЕКСА ПРИ ЗЛОКАЧЕСТВЕННОЙ МЕЛАНОМЕ

В обзоре обсуждается роль кадгерин/катенинового комплекса при злокачественной меланоме. Кадгерин представляет собой суперсемейство адгезивных молекул, среди которых наиболее изучен эпителиальный кадгерин (Е-кадгерин), выполняющий ключевую роль в норме и при инвазивном опухолевом росте и метастазировании. В ткани злокачественных меланом уровень экспрессии Е-кадгерина изменен, его снижение или отсутствие связано с инвазивным ростом и метастазированием опухоли. При образовании злокачественных меланом в меланоцитах отмечают замену экспрессии Е-кадгерина на таковую неврального кадгерина (N-кадгерина). Кроме того, коротко обсуждается роль плацентарного кадгерина (Р-кадгерина), эндотелиального кадгерина сосудов (VE-кадгерина) и недавно идентифицированного дисадгерина.

Ключевые слова: молекулы адгезии, кадгерин, катенин, дисадгерин, меланома.