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REVIEW

Changes in Regulation of Cell–Cell Adhesion during Tumor Transformation

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Abstract—Cadherin-mediated cell–cell adhesion defines the integrity of most tissues. Cell–cell adherens junctions are dynamic structures whose functional state is regulated by interactions of cadherin with β-catenin, p120, and actin cytoskeleton structures. Small GTPases of the Rho family and GTPase Rap1 play the central role in the formation and maintenance of cell–cell adhesion. Aberrant activation of signaling pathways, transcriptional repression of the E-cadherin gene, ectopic expression of N-cadherin, and disturbances in regulation of adhesive and transcriptional functions of β-catenin stimulate tumor progression.

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CELL–CELL ADHERENS JUNCTIONS

Cell–cell interactions play the most important role in embryonic development, differentiation, and tissue architecture regulation. Disruption of cell–cell adhesion during carcinogenesis is the basis for invasion and metastasis of tumor cells [1-5].

The main molecules of cell–cell adhesion are cadherins, transmembrane proteins of the classical cadherin family, which form in the presence of Ca^{2+} cell–cell adherens junctions (AJ) associated via the cytoplasmic plaque proteins with actin microfilaments [6]. Cadherins provide for mechanical cell–cell adhesion and regulate cell shape, segregation, migration, proliferation, and differentiation [7, 8]. In epithelial cells E-cadherin is expressed, whereas AJ in cells of other tissue types are formed by cadherins N, P, R, VE, etc. Cadherins are synthesized as precursors that undergo several posttranslational modifications including proteolytic cleavage. In particular, E-cadherin is transformed from a 135 kD precursor into a 120 kD molecule with N-terminal Asp135. Correct cleavage of precursors is necessary for construction of adhesive dimers [9].

The cadherin molecule incorporated into plasma membrane has extracellular, transmembrane, and intracellular regions. The extracellular region of classical cadherins consists of five domains (EC1-EC5), each of which is formed by 110 amino acids. There are four Ca^{2+}-binding sites between EC domains [10]. It is now assumed that trans-interactions of cadherin molecules are caused by binding of EC1 domains of adjacent cells via reciprocal interaction of Trp156 from one EC1 domain with a hydrophobic pocket of another EC1 domain [9, 11].

The cytoplasmic domain of cadherins is highly conserved and includes the membrane-adjacent site for cadherin binding to p120-catenin (p120) and C-terminal site for binding β-catenin, which regulate cell–cell adhesion [12]. Cadherins bind via β-catenin, plakoglobin, and α-catenin to actin filaments, which stabilize the structure of AJ [13, 14]. The interaction of E-cadherin–β-catenin–α-catenin–actin filaments in the region of cell–cell contacts is dynamic [15, 16].

DYNAMICS OF AJ FORMATION

The process of AJ formation can be arbitrarily divided into the following stages: mechanically weak trans-interactions of individual cadherin receptors bound by their cytoplasmic domains with β-catenin molecules; contact stabilization by formation of cadherin clusters after recruiting the cytoplasmic plaque proteins and bind-

Abbreviations: AJ) cell–cell adherens junctions; EGF) epidermal growth factor; EMT) epithelial-mesenchymal transformation; FGF) fibroblast growth factor; GEFs) guanine nucleotide exchange factors; HGF/SF) hepatocyte growth factor/scatter factor; PDGF) platelet-derived growth factor.

ing of actin filaments; contact maturation due to further actin accumulation in the contact region. The interactions of cadherin with actin are of no importance in the first steps of intercellular interaction, but are extremely important for contact stabilization [17]. Adhesive interactions, supported by the Ca^{2+}-independent binding of Ig-like nectins of adjacent cells play an essential role in stabilization of initial cadherin contacts [18].

Formation of cell–cell contacts is accompanied by structural rearrangements of actin cytoskeleton. These rearrangements are different in epithelial cells and fibroblasts and are defined by common organization of the actin cytoskeleton in the cells of two tissue types. In particular, when AJ of epithelial cells are formed, marginal actin bundle in the contact zone dissociates as the result of local breaks and ark-like bundles are formed at the lateral free cell edges [19, 20]. Further actin accumulation and formation of adhesion belts along the cell perimeter takes place during maturation of epithelial contacts. Formation of cell–cell contact of epitheliocytes is accompanied by inhibition of pseudopodial activity (contact paralysis) in the contact region and at free edges of the cells.

Fibroblast-like cells form AJ of different spatial organization from AJ of epitheliocytes. AJ of fibroblasts are most often formed by N-cadherin, are located in the region of overlap of the adjacent cell lamellas, and are characterized by radial organization. Such contacts are perpendicular to the contact border and are associated with short straight actin bundles [21, 22]. Formation and maintenance of radial contacts is defined by contractility of associated microfilament bundles, because inhibitors of actin-myosin contractility cause their disappearance. In fibroblasts, formation of AJ is not accompanied by inhibition of pseudopodial activity: lateral lamellae are formed at the free cell edges of the colliding cells, which may result in change in cell motility direction after their contact [22].

In the course of embryonic development as well as during metastatic tumor progression, the so-called epithelial-mesenchymal transformation (EMT) takes place, which results in transformation of epithelial cells into fibroblast-like ones. The effect of phorbol ether (TPA) on epithelial cells in culture can be used as a model for investigation of early EMT steps. Already 1-2 h later there begins destruction of the actin cytoskeleton typical of epitheliocytes, i.e. the disappearance of circular microfilament bundles accompanied by radical rearrangement of cell–cell interactions. In the course of cell–cell interaction, the cells form E-cadherin-containing AJ that have not tangential but radial organization characteristic of fibroblasts. In this case, pseudopodial activity is not stabilized after the AJ formation [23].

Actin polymerization *de novo* plays an essential role in formation of stable AJ [24-26]. Experiments with exogenous G-actin incorporation have shown that the labeled globular actin is accumulated in the region of newly formed AJ of epitheliocytes and is co-localized with E-cadherin within 5 min after transfer of the cells from the low-calcium medium into the high-calcium medium (calcium concentration ~1.8 mM) [27]. Actin polymerization begins from filament nucleation and following elongation. The protein complex Arp2/3 consisting of seven polypeptides plays the key role in nucleation of the branched network of actin filaments [28]. The available data show that the Arp2/3 complex is involved in formation of cell–cell contacts [26, 29]. The Arp2/3 activators N-WASP, WAVE2, and cortactin were shown to be necessary for the assembly of stable AJ [27, 30, 31]. These proteins are co-localized with cadherins in the regions of new AJ. Introduction into cells of a dominantly negative cortactin, lacking the F-actin-binding site, or unable to bind Arp2/3 or inhibition of the cortactin gene expression by a small interfering RNA (siRNA) results in inhibition of new AJ formation and destruction of already existing contacts [25]. The N-WASP inhibitor wiskostatin blocks the assembly of E-cadherin-containing AJ of epitheliocytes [27]. Inhibition of WAVE2 expression upon introduction of specific siRNA also resulted in distortion of actin recruitment and AJ disorganization [31].

Formins, able to nucleate polymerization of linear actin filaments and provide for their elongation, also contribute to formation of new actin structures in the region of cell–cell contacts [32]. Thus, the α-catenin-binding FMN1 is necessary for AJ formation and maintenance in keratinocytes [33]. Recently it has been also shown that another member of the formin family Dial, activated by the small GTPase Rho, is involved in AJ formation in epitheliocytes [34]. The formin-stimulated mechanism of actin filament growth is based on the ability of the formin dimer to bind in a stepwise manner to each next attached actin monomer using the FH2 domain. In this case, the filament plus-end appears to be protected against binding to capping proteins, whereas the formin dimer is rapidly translocated along the growing filament [35-37]. The formin domain FH1 is able to bind profilin, which can also stimulate filament growth due to efficient recruitment of actin molecules [35].

INVOLVEMENT OF SMALL GTPases OF Rho FAMILY IN AJ FORMATION

There are now numerous data concerning the involvement in AJ formation of small GTPases of Rho family (Rho, Rac, and Cdc42), regulating intracellular dynamics of actin cytoskeleton. It was shown that expression of dominantly negative mutants of *RhoA*, *Rac1*, and *Cdc42* genes as well as injection into cells of negatively dominant forms of their proteins disturbed formation of E-cadherin-containing contacts of MDCK epitheliocytes and keratinocytes [38, 39]. It was found that GTPases Rac1 and Cdc42 were recruited into zones of N- and E-

cadherin-dependent cell–cell adhesion [40-42]. GTPase Rac1, activated via phosphatidylinositol-3-kinase (PI3K), nectins, or via IQGAP1 [18, 43, 44] and regulating the Arp2/3-mediated actin polymerization, is of essential significance for AJ formation. Rac1 is activated via the lipid product of PI3K—phosphatidylinositol (3,4,5)-triphosphate (PIP3). PIP3 interacts directly with GEFs (P-Rex1, SWAP-70, Vav1, Sos1, and evidently Tiam1) activating Rac1 [44]. Rac1, in turn, is able to stimulate via proteins of the WASP family (N-WASP and WAVE2) the Arp2/3-mediated actin assembly in the zone of cell–cell contact. Since WAVE2 can form a supramolecular complex with Rac via IRSp53, it is assumed that the Rac–WAVE2–Arp2/3 pathway plays the leading role in the assembly of actin structures that stabilize cell–cell contacts [45].

Tiam1, a Rac1-specific GEF, plays an essential role in the regulation of assembly of AJ. Tiam1 was initially described as the invasive phenotype inductor of lymphoma cells. In epithelial cells, Tiam1 is accumulated in cell–cell contacts. The expression of Tiam1 in Ras-transformed epitheliocytes stimulates normalization of transformed phenotype and restoration of cell–cell adhesion. It was also shown that the effect of exogenous Tiam1 in epithelial cells depends on the cell substrate. Tiam1 activates motility of epitheliocytes grown on collagen and, in contrast, it stabilizes cell–cell contacts of epitheliocytes grown on fibronectin or laminin [46].

There are also data concerning the involvement of IQGAP1 in AJ stabilization. IQGAP1 contains binding sites for actin, calmodulin, the myosin light chain kinase, Rac1/Cdc42, Rap1, β-catenin, E-cadherin, and APC [47]. It is assumed that IQGAP1 inhibits GTP hydrolysis and stabilizes Rac1 and Cdc42 in the active state, and in this case IQGAP1 is an effector of Rac1 and Cdc42. Rac1 and Cdc42 inhibit the interaction of IQGAP1 with β-catenin, which stabilizes contacts [43].

Although there are data concerning the most important role of activated GTPases of Rho family in AJ assembly, relative contribution of different pathways, regulated by these GTPases, to cell–cell adhesion and assembly of actin structures in the contact zone is still unclear.

CELL–CELL ADHESION REGULATOR Rap1

The small GTPase Rap1 was first described as a suppressor of Ras-transformation [48]. The involvement of Rap1 in regulation of cell–cell contacts in mammals was found during studies of GEF for Rap1–DOCK4, inactivating mutations of which were detected in some lines obtained from human tumors. Human osteosarcoma cells that lost DOCK4 did not form AJ. In this case, introduction of DOCK4 or an active Rap1 restored formation of AJ and decreased metastatic activity of tumor cells [49]. The reappearance of AJ was also observed upon introduction of active Rap1 into Ras-transformed MDCK epitheliocytes. Besides, endogenous Rap1 activation blocks HGF/SF-stimulated cell dissemination and AJ disassembly [50].

Rap1 is now considered to be the key regulator of E- and VE-cadherin-mediated adhesion. Two models have been proposed for the participation of Rap1 in AJ assembly. According to the first model, in the initial steps of cell–cell contact formation trans-interaction of nectins activates the src-tyrosine kinase that phosphorylates C3G (GEF for Rap1) and recruits it onto the membrane, which results in the activation of Rap1 [51]. Another GEF for Rap1, PDZ-GEF1, is able to bind β-catenin and MAGI-1 and MAGI-2 proteins and can be involved in AJ maturation [50, 52]. It was shown that activation of small GTPases Rac1 and Cdc42 upon AJ formation depends on Rap1 activity [53, 54]. It is supposed that GEFs of small GTPases Rac1 and Cdc42 (Vav, Tiam1, FRG), regulating actin polymerization in the region of cell–cell contacts and thus stimulating contact maturation, are activated by Rap1 [54]. According to the second model, Rap1 activation by nectins recruits afadin/AF6 that binds to p120, which, in turn, inhibits E-cadherin endocytosis [55]. It is also supposed that Rap1 plays an important role in coordinated disassembly of cadherin-containing AJ and formation of cell–matrix focal contacts upon induction of EMT [56].

TUMOR SUPPRESSOR E-CADHERIN

It is now generally accepted that E-cadherin is the main suppressor of epithelial tumor invasion. Decrease or disappearance of E-cadherin expression is described in many human carcinomas [57, 58]. A single mutation of the E-cadherin gene can be responsible for transformation of adenoma to carcinoma. Expression of exogenous E-cadherin in cells of transformed epithelial lines significantly reduces their invasive potential and restores normal phenotype [59]. There are data concerning the inhibitory effect of the E-cadherin homophilic trans-interactions on cell proliferation via interaction of β-catenin, bound to E-cadherin at the plasma membrane, with epidermal growth factor receptor (EGFR). Interaction of cell–cell adhesion molecules with EGFR results in inhibition of EGFR phosphorylation at Tyr845, which, in turn, decreases activation of the ERK-independent signaling pathway via STAT5b activation [60-62]. The enhanced activity of receptor tyrosine kinases characteristic of many tumors can decrease due to binding of the growth factor receptor to the extracellular domain of E-cadherin [63].

In the course of tumor progression, epithelial cells undergo EMT during which cells acquire the fibroblast-like phenotype, the ability for directed migration, and dissociate from each other. These events are the basis for

invasion and metastasis of malignant cells. The decrease of E-cadherin expression leading to destruction of cell–cell contacts plays the most important role in EMT [64].

Inhibition of E-cadherin expression in tumors is achieved in three ways: by transcriptional repression or mutation of E-cadherin gene *CDH1*, as well as by hypermethylation of CpG islets of the gene promoter [65-69]. Histone H3 deacetylation of CpG islets was also found in some lines of epithelial tumors [70].

Transcriptional repression of the E-cadherin gene *CDH1* is the key regulator of EMT and is most often involved in carcinoma progression. *CDH1* transcription repressors belong to three families: i) Snail (SNAIL1, SNAIL2 (SLUG), SNAIL3); ii) ZEB1 (DeltaEF1)/ZEB2 (SIP1), and iii) TWIST/E47 factors bHLH interacting with the E-cadherin gene promoter [71-73]. The Snail family proteins regulate EMT in embryogenesis upon mesoderm formation, gastrulation, and neural crest formation. SNAIL1 overexpression in epithelial cells also stimulates EMT, which is revealed in acquirement by cells of ability for directed migration and for invasiveness, which was detected during investigation of cell invasion through a gel consisting of collagen IV [71]. It has been shown that in many human carcinomas, in particular, in gastric tumors, liver, colon, and ovary carcinomas, and breast cancer SNAIL1 expression correlates with inhibition of E-cadherin expression [74, 75]. SNAIL1 protein belongs to the family of transcription repressors containing four zinc fingers at the conserved C-terminus, which bind the latter by E2-boxes located near the site of *CDH1* gene transcription initiation [76, 77]. SNAIL1 repressor activity is defined by the SNAG domain at the N-terminus of the molecule and is regulated by the central domain, whose phosphorylation by GSK3β kinase alters the subcellular localization, stability, and activity of SNAIL1. Cooperation with LOXL2 stabilizes SNAIL1 by regulation of its binding to GSK3β [78]. SNAIL2 expression is detected in breast cancer, carcinomas of ovaries, colon, and in melanomas. Expression of SNAIL1 and SNAIL2 often correlates with poor clinical prognosis [78].

Multiple signaling cascades including the FGF, PDGF, Wnt, EGF, HGF/SF, Ras-MAPK, Ras/PI3K/AKT, TGFβ, and Hedgehog-GLI1 pathways (involved in EMT upon oncogene activation), hypoxia, and microenvironment regulate activity of the *CDH1* transcription repressors [79]. Transcription repressors ZEB1/ZEB2 were detected in gastric tumors, carcinomas of, pancreas, bladder, and ovaries. The TWIST factor is revealed in ductal breast cancer, bladder and prostate tumors, hepatocarcinomas, and melanomas. TWIST is now considered as a factor playing a key role in early stages of metastasis [78, 79]. TWIST also induces N-cadherin expression in prostate carcinoma cells [80].

Co-expression and sequential activation of transcription repressors Snail, ZEB1/ZEB2, and TWIST/E47 can be observed in epithelial tumors [72]. Binding sites of Snail and other repressors of the E-cadherin gene are overlapping. Comparative analysis of the affinity to E1/2-boxes of *CDH1* repressors SNAIL1, SNAIL2, and E47 has shown that in the presence in a cell of all three repressors their hierarchies by the extent of affinity and by prevalent contribution to repressor effect are observed. Different repressors can be involved in *CDH1* repression, specific for different types of tumors, or certain stages of tumor progression.

Transcription repressors modulate expression of the E-cadherin gene and of many different genes of epithelial cells. In particular, they decrease expression of the tight junction proteins occludin and claudin, desmosome protein plakophilin-3, cytokeratins 17/18, integrins α3/α4, and actin-binding protein gelsolin; they also change spectrum of catenin p120 isoforms [78, 81].

Recent studies of functioning of *CDH1* transcription repressors have shown that these proteins, contributing to EMT, are able to regulate expression of many genes by influencing tumor cell proliferation and survival, by inhibition of apoptosis, and by stimulation of multidrug resistance, which is important for tumor progression [78].

ROLE OF p120 IN CADHERIN STABILIZATION ON MEMBRANE

Along with other adhesion plaque molecules, p120 plays an important role in cell–cell adhesion by participation in cadherin clustering and endocytosis, and in N-cadherin transport onto the plasma membrane [82]. It has been shown in recent works that p120 is a key regulator of AJ stability. It was shown that p120 stabilizes the macromolecular adhesion complex by prevention of transmembrane cadherin internalization and thus by regulation of intracellular cadherin turnover [55]. The first direct indication that p120 is a central molecule regulating the adhesion function of cadherin was reported in analysis of the SW48 carcinoma cell line containing a mutation in the p120 gene. It appeared that in the absence of p120, transformed cells are not able to form compact colonies and cannot spread on the substrate covered with chimeric protein formed by the E-cadherin ectodomain bound to Fc-fragment of IgG. In these cells the amount of E-cadherin dramatically decreased, whereas the level of E-cadherin mRNA did not change. The loss of p120 caused internalization of membrane cadherin and its delivery to lysosomes with following proteolytic degradation. In this case, expression of exogenous p120 increased intracellular level of E-cadherin and restored cell–cell adhesion and cell spreading on the substrate covered with chimeric protein [83].

Two models of the E-cadherin endocytosis regulation with involvement of p120 are now being discussed. In the first model, p120 is considered as a capping molecule

connected with the cadherin tail and preventing the interaction of cadherin with the endocytosis machine. An alternative model suggests that p120 influences the stability of E-cadherin in AJ via interaction with small GTPases Rho, Rac, and Cdc42 [55]. An important role in ligation of E-cadherin molecules belongs to the cell–cell adhesion molecule nectin, which is involved in the assembly of a supramolecular complex by p120 recruitment onto the cytoplasmic tail of E-cadherin due to activation of small GTPase Rap1 and interaction with the actin-binding protein afadin [84].

It is still not clear which events serve as a launching moment for p120 dissociation from the E-cadherin cytoplasmic tail and following endocytosis. It is supposed that E-cadherin endocytosis begins after its phosphorylation on tyrosine, binding by E3-ubiquitin-ligase Hakai, and ubiquitin binding [85]. The E-cadherin phosphorylation and binding to Hakai can be prevented by p120 [55]. Recently it has also been shown that casein kinase 1 phosphorylates Ser846 of the E-cadherin cytoplasmic tail, thus promoting its internalization and weakening of cell–cell adhesion [86].

Cadherin endocytosis is triggered in response to growth factors, change in the blood vessel endothelium permeability caused by the growth factor VEGF due to alteration of VE-cadherin barrier function, and in response to oncogenic transformation [87-91]. The changes in cell–cell adhesion might be mediated by p120 phosphorylation. Thus, HGF/SF, EGF, and PDGF phosphorylate p120 via protein kinase Src, which results in destabilization of the E-cadherin/catenin complex [92-94]. The FGFR1 or met-receptors in the case of binding, respectively, to FGF or HGF/SF, are co-internalized with E-cadherin [87, 89]. Overexpression of MDM2, a negative regulator of tumor suppressor p53, contributes to the development of invasive phenotype. Recently it has been shown that E-cadherin is a substrate for MDM2, and upon its binding to the latter the processes of E-cadherin ubiquitination and endocytosis are triggered. Dominantly negative dynamin mutants, blocking endocytosis, disturbed the interaction of E-cadherin with MDM2 and decreased migration and invasive activities of MCF-7 carcinoma cells expressing exogenous MDM2 [95].

The decrease in p120 expression or complete disappearance of p120, regulating E-cadherin endocytosis, is found in many human tumors; in some tumors, a relationship between decreased levels of E-cadherin and p120 was detected [96]. Inhibition of p120 expression, change in intracellular protein localization (transfer into the cytoplasm and nucleus), appearance of the long isoforms of p120 typical of high-motility fibroblast-like cells, and the p120 binding to microtubules and Kaiso transcription factor might contribute to tumor progression. Inhibition of cell–cell adhesion and enhancement of migration ability are the main result of changes in regulation of E-cadherin endocytosis in transformed cells [63].

ADHESIVE AND TRANSCRIPTIONAL FUNCTIONS OF β-CATENIN

The E-cadherin–β-catenin complex is formed in endoplasmic reticulum and then is transported onto the plasma membrane [97]. In the case of AJ formation, β-catenin provides for link between cadherin and α-catenin and plays an important role in the maintenance of contact stability [13]. Tyrosine phosphatase PTP1B of adhesion complexes maintains β-catenin in its dephosphorylated state [98]. The distortion of β-catenin adhesive function is first of all caused by phosphorylation of tyrosines in positions 142 and 654, which results in disassembly of E-cadherin-containing complexes in the membrane. Phosphorylation of β-catenin at Tyr654 by c-src disturbs its binding to E-cadherin and destroys cell–cell adhesion [99, 100]. Phosphorylation of β-catenin was described upon Ras activation, and it is also characteristic of effects of some growth factors. Thus, EGF induces β-catenin and plakoglobin phosphorylation, resulting in breaking of E-cadherin binding to actin cytoskeleton and contact disassembly [60]. EGF receptors are overexpressed in many carcinomas, which may contribute to EMT due to β-catenin phosphorylation [63].

β-Catenin is also the most important component of cellular signaling pathways, in particular, of the Wnt-signaling pathway. In a complex with transcription factors TCF/LEF, β-catenin activates transcription of many genes, in particular of *myc*, cyclin D1 gene, *FGF18*, and *FGF20* [101-106]. An increasing amount of recent data show that adhesive and transcriptional functions of β-catenin are tightly connected and are involved in changes in tumor cell morphology and motility [107, 108]. Phosphorylation at tyrosine influences both adhesive and transcriptional functions of β-catenin: phosphorylation at Tyr142 in the case of BCL9-2 overexpression not only results in β-catenin release from AJ with subsequent EMT, but also enhances nuclear transcriptional activity of β-catenin [109].

β-Catenin significantly contributes to transformation via the Wnt-signaling pathway that begins from receptors of the Frizzled family. In the absence of signals β-catenin is recruited by a complex consisting of APC protein, axin, GSK3β kinases, and casein kinase 1. Phosphorylation of the β-catenin N-terminus at serine–threonine in this complex serves as a signal for its ubiquitination and subsequent proteosomal degradation [110-112]. Canonical Wnt-signals induce the Frizzled–Dishevelled complex interaction with LRP5/6 co-receptors, which results in axin recruitment to the plasma membrane, of β-catenin degradation, and its transfer to the nucleus in a complex with transcription factors TCF/LEF [113, 114]. It has recently been found that proteins BCL9 and BCL9-2 of the Legless family play an important role in the transcriptional function of β-catenin by binding the latter to co-activators

PYGO1/2, which is necessary for translocation of β-catenin into the nucleus [115, 116]. BCL9-2 overexpression induces malignant transformation of epithelial cells *in vitro* and is detected in human colon carcinomas [109, 117]. However, even in the case of the Wnt-signaling pathway activation β-catenin can be sequestered by E-cadherin and excluded from transcriptional regulation [118].

APC, *CTNNB1*, and *AXIN* mutations, activating the canonical Wnt-pathway, are detected in human colorectal carcinomas, hepatoblastomas, and melanomas [119-121]. Mutations of *APC* are responsible for development of familial adenomatous polyposis coli and are detected in 85% of cases of sporadic colorectal cancer [122]. It has also been shown that mutations of *APC* via GEF of small Rac GTPase, Asef, contribute to the enhanced migration activity of the colon carcinoma cells [123].

The serine–threonine kinase GSK3β, involved in degradation of both β-catenin and the cadherin transcription repressor SNAIL1 [124], is also a key component of the FGF signaling pathway playing a noticeable role in control of tumor cell proliferation, differentiation, migration, and survival. The activation of the FGF signaling pathway in which Akt phosphorylates GSK3β at Ser9 results in down-regulation of GSK3β activity with subsequent increase in SNAIL1 level. SNAIL1 represses E-cadherin expression, which results in release of β-catenin from adhesion contacts and its translocation into the nucleus [125-127]. Since *FGF18* and *FGF20* are effector genes of the Wnt-signaling pathway, activation of the latter upon transformation triggers the FGF signaling system as well [128, 129].

Thus, multiple pathways of deregulated adhesive and transcriptional functions of β-catenin play an important role in different stages of carcinogenesis.

PARTICIPATION OF N-CADHERIN IN CELL–CELL ADHESION: ITS ROLE IN TUMOR CELL INVASION AND METASTASIS

Adherens junctions in nervous and connective tissues, myocardium, bone, and cartilage are formed by N-cadherin [130]. Measuring of the strength that need be applied for separation of cells in contact has shown that N-cadherin-containing cell–cell contacts are significantly weaker than those involving E-cadherin [17]. These differences can be determined either by cadherin binding to different p120 isoforms or by the extent of p120 phosphorylation in different adherens junctions [130]. In the case of formation of N-cadherin-containing contacts, the contribution of specific Fer-kinase is of great importance. Upon binding of N-cadherin molecules of adjacent cells, Rac-dependent cortactin recruitment into the region of cell–cell contacts and cortactin phosphorylation by Fer-kinase resulting in adhesion enhancement occurs [131].

At the same time, data continue to appear showing that N-cadherin plays a decisive role in invasion and metastasis of epithelial tumor cells by stimulation of their migration. In many human carcinomas, including breast cancer, thyroid, bladder, and prostate carcinomas, aberrant expression of N-cadherin has been detected along with inhibition of E-cadherin expression. Re-expression of N-cadherin, found during embryogenesis in melanocytes only at the stage of neural crest formation, is also described in metastatic melanomas [132]. It was also shown *in vitro* that N-cadherin expression by epithelial cells, independently of the E-cadherin expression level, causes EMT and stimulates cell migration activity [133]. Exogenous N-cadherin expression in MCF-7 breast cancer cells resulted in metastases to lymph nodes, liver, and lungs after injection of these cells into nude mice [134]. It can be supposed that the proinvasive effect of N-cadherin expression in epithelial tumors is explained by the N-cadherin-mediated tumor cell interactions with stromal fibroblasts that, according to recent data, are involved in collective invasion of carcinoma cells [135]. It has been also shown that N-cadherin interacts with FGF receptors. This inhibits their internalization and results in MAPK-cascade activation and expression of metalloproteases [133, 136]. Recent data also show that in HT-1080 cells N-cadherin/β-catenin form via NHERF a complex with receptors of PDGF that modulates actin cytoskeleton and contributes to cell motility [137]. Thus, aberrant expression of N-cadherin in carcinomas can be involved in EMT during invasion.

The data show that AJ are of key significance for the tissue architecture. The formation, stabilization, and maturation of AJ are first of all defined by their close interaction with the actin cytoskeleton structures as well as by small GTPases regulating trans-interactions of cadherin molecules, their endocytosis, and actin dynamics in the region of cell–cell adhesion. In connection with widely described disruption of cell–cell adhesion at different stages of carcinogenesis, in particular in the case of EMT, studies of molecular events accompanying oncogene activation and resulting in rearrangements of AJ organization up to their complete disappearance become most important. Investigation of such rearrangements, changes in regulation of adhesive and transcriptional functions of the cell–cell adhesion molecules, and their relationships with changes in cytoskeleton structures during malignization will lead to better understanding of events that are the basis of neoplastic transformation.

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