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ECCU (E-cadherin/catenin) complex and its role in carcinogenesis

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Abstract

Introduction:

One of the main characteristics of cancer is uncontrolled cell proliferation as well as loss of cells adhesion in the case of metastases. Cadherins and catenins are the molecules responsible for cell-to-cell interaction. Together, they form a complex called ECCU (E-cadherin/catenin complex) which maintains the proper tissue structure. However, an impairment in its functioning can result in many adverse health effects, such as cancer promotion.

Purpose:

To evaluate the potential role of ECCU complex in carcinogenesis.

Materials and methods:

We performed the database research using PubMed, Springer Link and ResearchGate and we made review and meta-analysis of relevant studies. We searched for studies analyzing the relationship between ECCU complex and carcinomas development.

Results:

ECCU takes part in many cell processes and pathways, such as Wnt/Wingless-signaling pathway or EMT/MET processes. It interacts with various molecules, for instance p27 protein or transcription factors. Aberrations in the expression of ECCU components is related to carcinoma promotion, shorter survival rate of patients and poor differentiation of the tumor.

Conclusions:

A role of the ECCU complex is complicated, however there is a clear correlation between loss of cell adhesion and carcinoma promotion and progression. The complex can be a possible target of anti-cancer therapy in the future; it is also under investigations as a marker of the disease, however it is questionable.

Key words: E-cadherin; catenin; ECCU complex; carcinogenesis; adhesion

Introduction:

Carcinoma is defined as an uncontrolled proliferation of cells, caused mainly by the mutations in proteins of cell cycle[1]. Carcinogenesis can occur due to genetic predispositions or occupational factors; the mechanism remains unknown. A crucial process in malignant transformation is the loss of cell adhesion, which results in the dissemination.

CAMS are defined as "cell adhesion molecules". The crucial role of CAMS is cell adhesion, keeping the structure of the tissue and cell-to-cell interaction[2]. They also take part in embryogenesis, cell migration, coagulation, and, if any aberration occur, in carcinogenesis. There are four main types of them – integrins, cadherins, immunoglobulin superfamily and selectins. Integrins are responsible for cell-to-cell and cell-to-extracellular matrix communication; immunoglobulin superfamily are a part of the immune system, selectins take part in the inflammation process; cadherins are involved in cell-to-cell communication and junction

Cadherins are transmembrane glycoproteins that are calcium-dependent. As it was mentioned, they control adhesion of cells[3]. Each of them has five extracellular domains performing interactions and a tail engaged in signals transduction.

Classical cadherins of vertebrates are differentiated into two groups – type I and type II, according to the presence of a HAV (histidine-alanine-valine) sequence[4] in the first EC domain. There are 5 cadherins belonging to the group of type I - CDH1 (E-cadherin), CDH2 (N-cadherin), CDH3 (P-cadherin), CDH4 (R-cadherin), and CDH15 (M-cadherin)[5]. Among these, the most known is E-cadherin (L-CAM, Uvomorulin), is responsible for tight (adherens) junctions; it is expressed mainly on epithelial cells. It is encoded by CDH1 gene.

β-catenin is a protein encoded by CTNNB1 gene and has two functions – it regulates both gene transcription and cell adhesion. In many studies it was suggested that aberrant expressions of β-catenin are correlated with cancers, for example colon cancer or hepatocellular carcinoma[6]. When there is no pathology, this protein is bound within the ECCU complex and if it is not, it is phosphorylated and degraded with an ubiquitin-mediated way by a complex composed of APC, Axin, Glycogen Synthase Kinase 3 beta (GSK3β) and casein kinase 1α (CK1α).

When E-cadherin and β-catenin are linked together, there is a complex called ECCU. ECCU contains α-catenin and $p120^{ctn}$ protein as well in order to regulate cadherin expression[7]. This complex is crucial in cell adhesion and maintenance of the proper tissue structure.

The complex takes part in two processes – EMT (the epithelial to mesenchymal cell transition) and, the opposite, MET (the mesenchymal to epithelial cell transition). In normal conditions, EMT process takes part in embryological development and tissue regeneration. However, when any aberration occur, it is involved in organ fibrosis and cancer metastases. Cells that undergo EMT are non-polar, cell adhesion is reduced, the E-cadherin expression is reduced and invasion ability of cells is improved. During EMT cells lose their epithelial phenotype, gaining migration and invasion ability. In many carcinomas, malignant transformation is related to the loss of cell adhesion and gain of a mesenchymal phenotype.

Purpose:

To evaluate the potential role of E-cadherin/catenin complex in carcinogenesis.

Materials and methods:

We performed the database research using PubMed, Springer Link and ResearchGate and we made review and meta-analysis of relevant studies. We searched for studies analyzing the relationship between ECCU complex and development of tumors.

Results:

Aberrations in the functioning of ECCU complex are related to carcinomas[8], for example cancers of the digestive tract or renal cancers[9]. Impaired functioning of the complex can be achieved through various ways, there can be both genetic mutations as well as epigenetic events[10]. It is widely known that CDH1 gene mutations result in lobular breast cancer as well as diffuse gastric cancer[11].

Cadherin switching is a very interesting process, referring to the change and reduction of E-cadherin expression to N-cadherin expression. This change is a part of EMT way. It was proved that switching leads to increased invasion and motility of cells, however it can be related more to the presence of non-epithelial N-cadherin. For example, N-cadherin

promotes antiapoptotic protein Akt/PKB, stabilizes β-catenin and inactivates the proapoptotic Bad protein in melanoma[12].

E-cadherin can be also called as a „growth supressor". It induces the cell cycle inhibition through positive regulation of p27 protein, which controls proper cells' proliferation by halting cyclin/cyclin-dependent kinase (CDK)[13].

What is more, E-cadherin is correlated with CD44 levels. CD44 is an antigen and multifunctional glycoprotein, which acts as a receptor for many ligands. The interaction with ligands of the extracellular matrix not only maintains tissue integrity, but also promotes invasion processes engaged in metastases. CD44 is considered as a marker of cancer stem cells[14]. Its overexpression significantly corresponds with advanced stages of tumor and increases metastatic potential. In some studies, low expression of E-cadherin and high CD44 expression was related with poor differentiation[15] and short survival[15]. The upregulation of CD44 molecule and downregulation of E-cadherin promoted invasion in esophageal carcinoma[16].

Besides taking parting in the ECCU complex, β-catenin is the main mediator of Wnt/Wingless-signalling pathway. This pathway regulates embryogenesis, cell proliferation and differentiation. Aberrations or dysregulation to the pathway can result in metabolic

diseases as well as development of carcinomas. There are two pathways of Wnt/Wingless-signalling pathway transducing the signal - one of them is canonical and depends on β-catenin, whereas the other is non-canonical and independent[17]. Molecules taking part in the canonical way are β-catenin, Glycogen Synthase Kinase 3 beta (GSK3β), adenomatous polyposis coli (APC), Dsh, AXIN and T-cell factor (TCF)/lymphoid enhancement factor (LEF).

When there are no ligands of the pathway, β-catenin remains at a low level which is possible due to the UPS (ubiquitin proteasome system). Catenin is bound by a complex responsible for destruction, that contains APC and AXIN. Then, a molecule undergo phosphorylation by casein kinase 1 (CK1) and GSK3β and the whole process is finished when β-catenin is ubiquitinated and its degradation occurs.

However, when the expression of the pathway is abnormal or some genetic mutations to β-catenin or destruction complex occur, the complex responsible for destruction is inactivated. β-catenin is then stabilized and accumulate in the cytoplasm of an epithelial cell. Subsequently, it is moved to the nucleus, where it binds to the TCF/LEF1 (a group of transcription factors). When its bound, it activates target genes of the pathway that regulate cell apoptosis and proliferation, for instance oncogenes like *CyclinD-1* or *c-Myc*[18]. What is more, β-catenin also interacts with molecules engaged in the progression and development of cancer, such as p300/CBP, TATA-box binding protein, TBP, Reptin52, MUC1-C, SOX10, FOXM1 or yes-associated protein 1 (YAP1)[6].

It was proven that in some cancers[19,20], such as breast cancer, colorectal carcinoma, hepatocellular carcinoma or melanoma, there is an accumulation of β-catenin in the nucleus of the cell. Also, mutations in the APC suppression gene, that resulted in the aberrant expression of Wnt pathway, were studied in colon carcinoma[21].

Discussion:

E-cadherin binds to catenins to form a complex called ECCU that is responsible for cell adhesion. When there is any aberration to the functioning of the complex or its expression is reduced, cells loose their contact. Loss of cell adhesion can result in metastases or malignant transformations of the tumor, as well as uncontrolled proliferation. It was proven that decreased expression of the ECCU complex occurs in some cancers[22].

ECCU is involved in carcinogenesis in various ways - cadherin switching, upregulation of p27 protein, correlation with CD44 antigen. What is more, ECCU takes part in the EMT process, widely related to carcinogenesis and fibrosis, in pathological conditions. During this course, cells gain invasive properties, there is a loss of cell adhesion and disorder of structure proper for epithelium. ECCU is also involved in a signaling pathway Wnt/Wingless. The dysregulation or excessive expression of the pathway was associated with carcinoma development in many studies[23].

There could be a possibility of using ECCU complex as a marker, however it is still under further investigation and its questionable. Aberrations and reduced expression of this complex correlates clearly with poor survival rate and poor differentiation[24] of the tumour; it can also be an early symptom of digestive tract tumors.

ECCU complex seems to be attractive in terms of becoming a target of anti-cancer therapy. It was suggested that renovation of the complex could have anti-invasive properties. Some

medicaments were tested - nonsteroidal anti-inflammatory drugs such as aspirin or indomethacin[25]. However, more clinical trials are needed, no drugs have been approved due to adverse effects.

Conclusions:

To conclude, ECCU is related to the cancer development. Reduced expression of this complex corresponds with the loss of cell adhesion, which can result in the malignant transformation and morphogenetic tumour changes. Disorders in E-cadherin expression correlates with high malignancy level, poor differentiation, distant metastases and poor survival rate.

ECCU could be used as a marker of an early disease or be a target of an anti-cancer therapy, however it is still under investigation.

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