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The importance of selected cell adhesion molecules in thyroid cancer

Magdalena Urbańczuk[1], Marcin Urbańczuk[2], Tomasz Tuzim[3], Katarzyna Schab[4], Kamila Tuzim[1], Marcin Lewicki[5]

[1]Chair and Department of Clinical Pathomorphology, Medical University of Lublin, Poland
http://orcid.org/0000-0002-2718-8213
http://orcid.org/0000-0002-3748-1579
[2]Chair and Department of Family Medicine, Medical University of Lublin, Poland
http://orcid.org/0000-0002-5736-1726
[3]Sanus Specialist Hospital, ul. Wojska Polskiego 4, Stalowa Wola, Poland
https://orcid.org/0000-0002-7793-0156
[4]Chair and Department of Clinical Immunology, Medical University of Lublin, Poland
http://orcid.org/0000-0001-8516-6971
[5]Chair and Department of Epidemiology and Clinical Research Methodology of Medical University of Lublin, Poland
http://orcid.org/0000-0003-1906-9326

Abstract

Thyroid cancer is the most common malignant tumour of the endocrine system. It accounts for ca. 2% of all malignant tumours in the world, ranking it 16th in the overall classification. Its most common histology type is the papillary carcinoma originating from the epithelial tissue, which embraces approx. 50-80% of all cases.

The epithelial tissue cells in normal conditions are closely interconnected by means of intercellular interactions. The adhesion process is regulated by a series of molecules, called cell adhesion molecules (CAMs). The main representatives of this group, which are increasingly better known and characterised, include the following: E-cadherin, β-catenin, CD44 and CD31 glycoproteins. CAMs regulate the course of many processes, such as differentiation, migration and growth of cells, but they also participate in the transmission of signals to the inside of the cell. Changes in the expression of cell adhesion molecules affect the disruption of the adhesion process. The recent years have seen many scientific reports on the importance of CAMs in the course of neoplastic transformation. It has been proved that abnormalities of CAM expression in many malignant tumours, including the thyroid cancer, are closely related to the increased primary invasion, distant metastasis and worse prognosis. These observations suggest that individual cell adhesion molecules may be used in the future as markers in the diagnostic process of thyroid cancers.

Key words: cell adhesion molecules, thyroid cancer

Introduction

Cell adhesion molecules (CAMs) are a diverse and very complex group of cell membrane glycoproteins. Three components may be distinguished in their structure: the intracellular component combined with the cytoskeleton, the extracellular part showing receptive properties and the transmembrane component. Adhesion molecules can act as receptors or as ligands for the respective receptors. The role played by CAMs in physiological conditions entails the following: control of a number of processes conditioning the ensuring of tissue continuity, regulation of mutual interactions between cells, as well as of the interactions between the individual cells with the elements of extracellular matrix (ECM) [1,2,3,4]. Adhesive molecules play an important role in numerous physiological and pathological

processes. Their importance in the course of embryogenesis and organogenesis has already been proven. They participate in the transmission of signals from the external environment to the inside of the cell, thereby regulating such phenomena as growth, proliferation, migration, cell differentiation and apoptosis [3]. They are also credited with having a significant impact on the immune system.

Dale Coman was the first scientist to get interested in the phenomenon of intercellular adhesion; in 1944 he analysed the behaviour of squamous cell carcinoma of the lip. Based on his observations, he found that squamous cells adhere closely to one another, and any disturbances in cellular connections are related to cell migration and creation of metastases [5,6]. Since then, numerous scientific reports have been published in the reference literature on the importance of cell adhesion molecules in neoplastic transformation, in progression of malignant tumours and the formation of distant metastases. Any changes in CAM expression affect the disruption of the adhesion process. This has been proven to lead to increased proliferation and migration of tumour cells. In addition, some adhesion molecules stimulate the angiogenesis process and initially facilitate the tumour cell adhesion to the walls of the blood vessels and then they help them pass through these walls. All these phenomena are conducive to an increased invasion of the primary focus on the surrounding tissues, as well as the formation of distant metastases [7,8,9,10]. Depending on the characteristics of the function, the function performed and the impact on specific cellular processes, CAMs can be divided into several main groups: integrins, selectins, cadherins, immunoglobulin-like molecules and CD44 proteins [8, 11].

Epidemiology of Thyroid Cancer

Thyroid cancer is the most common endocrine cancer. The recent years - probably due to the increased prevalence of imaging examinations - have seen an increased incidence of this cancer. According to the data presented by the National Cancer Registry in Poland, 3144 cases of thyroid cancer were detected in 2014, with a five-fold predominance in the female population in relation to men (respectively 2631 in women and 513 in men). For comparison, in 2000, 1457 new cases of thyroid cancer were diagnosed in Poland [12]. According to GLOBOCAN data, in 2012, thyroid cancer ranked 12th in terms of prevalence in Europe and 16th in the world, which is 2% of all malignancies [13]. Unfortunately, the forecasts for the coming years are not optimistic. When analysing the incidence of malignant tumours in the

world population, it is estimated that by the year 2030, thyroid cancer will be the fourth most common cancer. Only breast cancer, lung cancer and prostate cancer will precede it [14].

Aim of the Study, Materials and Methods

The aim of this study was to present and characterise selected adhesion molecules and to discuss their significance for the progression of malignant thyroid tumours and the formation of distant metastatic foci. To do this, the latest scientific reports from the PubMed database have been analysed.

Discussion

Characteristics of Selected Adhesion Molecules

Cadherin is a relatively recently discovered, heterogeneous group of transmembrane glycoproteins. It consists of several dozen different adhesion molecules, arranged in 6 main groups: classical cadherins (type I), atypical cadherins (type II), desmosomal cadherins (desmoglein, desmocollins), protocadherin, Flamingo cadherin and other unclassified cadherins [15]. Until now, most information has been gathered about the group of classic type I molecules, among which the cadherin E and N are best known. These glycoproteins are characterised by their ability to create calcium-dependent homophilic interactions with identical molecules located on another cell. The cadherins are located in places called the closing or constricting rim. In their construction, three main components should be distinguished: extracellular, transmembrane and intracellular domains. In the extracellular part, in addition to properly arranged repetitions, certain calcium ion binding sequences are found, which is an indispensable element in the formation of homophilic intercellular adhesion. The intracellular part interacts with the actin filament of the cytoskeleton of the cell by binding to the catenin complex and the p120 protein [8,16,17].

E-Cadherin, otherwise called epithelial (also referred to as uvomorulin or L-CAM) was discovered first, therefore its properties have been best investigated so far. It plays a key role in the adhesion of epithelial cells, maintaining tissue integrity and controlling cell polarisation [18]. It is a glycoprotein with a molecular weight of approx. 120kDa, encoded by the CDH1 gene located on the arm of the long chromosome 16 in position 22.1 (16q22.1) consisting of 16 exons [19]. Another cadherin glycoprotein playing an important role in thyroid cancer is N-cadherin (also referred to as neural cadherin, A-CAM), which is expressed mainly in

nervous tissue and muscles. It is coded by the CDH2 gene located in position 12.1 on the long arm of chromosome 18 (18q12.1) [20,21].

Other important molecules involved in the neoplastic transformation process include catenins. This group includes 4 cytoplasmic proteins (α, β, γ, δ - catenin) that form complexes with cadherins and thus participate in the adhesion process [22, 23]. An important role in cancer transformation is attributed to β-catenin, hence this molecule will be described in the following part of the paper. β-catenin is a multifunctional protein used in embryogenesis, organogenesis and maintenance of cellular homeostasis [24]. It participates in the separation of centrosomes during mitosis, while it also participates in intercellular adhesion and plays a key role in the functioning of the classical path of the Wnt (wingless type) pathway, influencing the expression of different genes, and thereby also affecting such cellular processes as proliferation, differentiation, puberty but also neoplastic transformation [25,26,27]. β-catenin is a protein composed of 781 amino-acids with a molecular weight of approx. 92kDa, encoded by the CTNNB1 gene located on chromosome 3 (3p21). The structure of this protein is based on 3 major domains: central, N-terminal and C-terminal [28]. The importance of β-catenin in the formation of tumours is related to its function in the Wnt/ Wingless/ βkatenin signalling pathway. A specific regulator of this path is the APC protein (adenomatous polypus coli), which interacts with axsin and 3β glycogen synthase kinase (GSK-3β). The resulting complex binds to the β-catenin, leading to its degradation through phosphorylation and ubiquitination [24]. The activation of the classical pathway occurs as a result of the combination of the Wnt ligand with the Frizzled receptor. Changes that occur in the cell as a result of this process lead to inhibition of the β-catenin protein degradation and, consequently, to the stabilisation of its molecule and its accumulation, initially in the cytoplasm, and then in the cell nucleus, where it forms a complex with the TCF/ LEF transcription factor (T cell factor/ lymphoid enhancer factor). The resulting complex activates the transcription of many different genes involved in the regulation of important cellular processes, such as proliferation, differentiation, maturation [26, 27, 30, 30, 31, 33], while it also stimulates a number of oncogenes, such as C-myc or cyclin-D1 [34,35]. Furthermore, it has been described in the reference literature how the TCF/ β-catenin complex formed has an effect on the incidence of increased VEGF concentration (vascular endothelial growth factor), and, thus, it stimulates the development of angiogenesis necessary for tumour growth and the formation of distant metastases. Another effect of the increased accumulation of β-catenin in the cell nucleus, which in turn impacts the increased tumour invasion by facilitating the

growth and infiltration of the tumour, is the activation of the genes responsible for encoding metalloproteinases [36,37,38,39].

The expression of the CD44 molecule is associated with the biological aggressiveness of many malignancies. CD44 proteins are glycoproteins belonging to one of the groups of adhesion proteins. The CD44 molecule is most often found in its standard form - that of CD44s. The expression of the CD44 molecule has been confirmed on many types of cells: lymphocytes, granulocytes, nephritic mesangial cells, glial cells and epithelial cells. CD44 is involved in many cellular processes, it participates in the activation of lymphocytes in inflammatory reactions, in interactions between cells, in interactions between cells and extracellular matrix, in cellular migration as well as in tumour proliferation and formation of metastases [40,41]. CD44 is encoded by a single gene composed of 20 exons (10 standard and 10 variables ones) which is located on chromosome 11 (11p13) [42]. The polymorphism of CD44 proteins results from the alternative folding of single-gene exon variables. As a result, a number of CD44 isoforms are formed with differences in the structure of the extracellular domain (CD44v) [43].

In tumour invasion and metastases formation, glycoproteins that affect the angiogenesis process, such as CD31, are also of crucial importance. CD31 glycoprotein (or PECAM-1 - a cell adhesion molecule of platelets and endothelium) belongs to the immunoglobulin superfamily and is a component of class I adhesion molecules. It is coded by a gene located on chromosome 17 (17q23), and its molecular weight is about 130kDa [44]. The expression of CD31 was observed, inter alia, on vascular endothelial cells and on the surface of tumour cells [45, 46, 47]. Its characteristic feature is the participation in cell adhesion; there are also literature data available on the participation of CD31 in the formation of blood vessels and its role in transmitting the signal inside the cell and inhibiting the process of apoptosis [48,49].

The Role of Selected Adhesion Molecules in Thyroid Cancer

In the process of neoplastic transformation, there is a gradual disappearance of contact between individual cells, which leads to their separation from the primary focus and migration, which results in the formation of metastatic foci. Through their involvement in angiogenesis and inhibition of the process of apoptosis, adhesive molecules are involved in tumour invasion and metastases formation. The scientific literature features data on the importance of the above-described adhesion molecules in thyroid cancer.

Researchers have observed reduced expression or no expression of the E-cadherin molecule in many malignancies. Similar observations apply to papillary carcinoma of the thyroid. In 2015,

Cheng et al. published an article in which they studied the expression of E-cadherin in 91 cases of papillary thyroid cancer. They confirmed the reduction of E-cadherin expression in 84.6% of the examined thyroid cancer cases. The reduction of E-cadherin expression in thyroid papillary cancer cells was statistically significantly correlated with the occurrence of metastases in the nodes ($p = 0.010$) [50]. Ivanova et al. (2017) studied the expression of E-cadherin and β-catenin in 112 people with epithelial carcinomas of epithelial origin. They showed that the stage of papillary cancer of the thyroid gland correlates with the level of E-cadherin expression in tumour cells. In patients with a higher stage of cancer (III and IV), the level of E-cadherin expression was lower than in patients with stage I and II severity. They also observed differences in the level of E-cadherin expression in differentiated thyroid cancers compared to anaplastic cancer. They confirmed that significant expression of the E-cadherin molecule in thyroid cancer is associated with a lower risk of metastases development [51]. Similar conclusions were obtained by Naito et al. in 2001 after analysing 64 cases of thyroid cancer, of which 53 were papillary cancers. After conducting the study, they observed much lower E-cadherin expression in the thyroid papillary carcinoma material compared to normal thyroid tissue. In the case of papillary cancers with present E-cadherin expression, no lymph node metastases were observed [52]. In their study published in 2015, Ceyran et al. showed no expression of E-cadherin in the studied papillary carcinomas of the thyroid ($p <0.005$), while in the studied benign lesions (follicular and dysplastic tumours), the expression of this molecule was significantly increased ($p <0.005$). The lack of E-cadherin expression was significantly more commonly ($p <0.05$) associated with the occurrence of metastases, the invasion of the tumour capsule, the presence of multiple tumour foci and the tumour size> 1 cm. The lack of E-cadherin expression was found in 92% of cancers with capillary infiltration, whereby 100% of lesions showed the presence of metastases to the lymph nodes, 95.3% of the tumours had a multifocal form and 93.3% of the tumours had a diameter> 1 cm [53]. Similar observations regarding the correlation between the loss of E-cadherin expression and unfavorable prognostic factors have been demonstrated by other authors [54,55,56,57].

In 2004. a work was published (authored by Rezk et al.), in which the authors assessed the expression of β-catenin in thyroid malignant tumour cells (53 cases of papillary carcinoma, 46 cases of variant follicular papillary carcinoma, 10 follicular carcinoma) and follicular adenoma (24 cases). They showed strong staining confirming the expression of β-catenin within the cytoplasm and cell nucleus, and weak staining within the cell membrane in the

material originating from malignant tumours. In most cases of follicular adenomas (76%) and in the control group (normal thyroid tissue), clear staining was observed within the cell membrane as opposed to poor expression in the cytoplasm of the cell [58]. Garcia-Rostan et al. examined material obtained from 145 thyroid tumours. They observed that in all 111 cases of thyroid cancer, significantly reduced expression of β-catenin within the cell membrane was present. In addition, they showed that the reduction of β-catenin membrane expression is associated with the loss of tumour differentiation [59].

Figge et al. published a study in which they confirmed high expression of the CD44 molecule in thyroid papillary carcinoma cells (97% of all cases). In the other thyroid carcinomas, the expression concerned about half of the cases. In addition, in papillary carcinoma, the thyroid assessed the presence of variant 6 of the CD44 molecule (CD44v6), the presence of which is associated with the existence of metastases and cases of cancer recurrence following surgery. They confirmed the expression of CD44v6 in all cases of papillary carcinoma of the thyroid undergoing such an evaluation [60].

Many publications have confirmed the more invasive nature of thyroid papillary carcinoma and the presence of its metastases in patients with the presence of the BRAF V600E mutation in tumour cells. In 2011, Durante et al. studied the presence of BRAF V600E mutations correlated with the presence of proangiogenic molecular markers (including CD31) in papillary carcinomas of the thyroid gland. In all cases of papillary thyroid carcinoma, the presence of CD31 positive microvessel density (MVD) was noted inside the tumour, as well as in the tumour tissue, compared to a normal thyroid tissue. A larger MVD was also observed in the case of cancer with a confirmed BRAF V600E mutation, however, without showing a statistically significant difference [61].

Conclusions

CAMs regulate the course of many processes, such as differentiation, migration and growth of cells, but they also participate in the transmission of signals to the inside of the cell. Changes in the expression of cell adhesion molecules affect the disruption of the adhesion process. Scientific reports published in recent years prove the importance of CAMs in the course of neoplastic transformation. The relationship between abnormal CAM expression in thyroid carcinomas and increased primary focus invasion, distant metastases formation as well as worse prognosis was confirmed. The research conducted so far will allow for a future use of the expression of selected CAMs as markers in the diagnostic process of thyroid cancer.

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