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Expression of immunoglobulins in human epithelial tumors and their potential role in carcinogenesis

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ABSTRACT

The traditional view on immunoglobulin (Ig) production only by B-lymphocytes and plasma cells has been revisited. Non-lymphoid tumor cells can also synthesize and secrete Ig with unidentified specificity. Expression of Ig genes was detected in the cells of malignant neoplasms of epithelial origin, such as breast carcinoma, colorectal cancer, prostate cancer, as well as in epithelial tumor cell lines. mRNA of the IgG1 heavy (H) chain constant region, sterile Iɣ-Cɣ transcript, H and light (L) chains of IgG, V(D)J recombination of H and L chain gene segments, as well as RAG1 (recombination-activating gene 1) and RAG2 enzymes, which are required for V(D)J recombination, were found in cancer cell lines and resected carcinoma tissues. IgG produced by cancer cells can be involved in the invasion and metastasis of these cells through interaction with E-cadherin, as well as with the metastasis-associated protein MTA1. Tumor-derived IgG plays an important role in malignant progression via activation of platelets by interacting with their FcγRIIa receptors and inducing the production of low levels of reactive oxygen species. The level of IgG in malignant neoplasms is positively correlated with proliferation markers, stage of progression, and growth and survival of the tumor. These data modernize the current views on the mechanisms of carcinogenesis and create the basis for the search for new diagnostic and prognostic markers in malignant neoplasms, as well as methods of their target therapy. Further in-depth studies of the phenomenon of Ig production by tumor cells will contribute to more effective practical application of the accumulated knowledge in this field.

Key words: immunoglobulin expression, cancer, non-lymphoid cell-derived immunoglobulin, cancer-derived immunoglobulin, carcinogenesis, metastasis.

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Экспрессия иммуноглобулинов в эпителиальных опухолях человека и их потенциальная роль в канцерогенезе

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РЕЗЮМЕ

Традиционное представление о продукции иммуноглобулинов (Ig) только В-лимфоцитами и плазматическими клетками в последнее время подвергается ревизии. Клетки нелимфоидных опухолей также могут синтезировать и секретировать Ig неидентифицированной специфичности. Экспрессия генов Ig выявлена в клетках злокачественных новообразований эпителиального происхождения, таких как карцинома молочной железы, колоректальный рак, рак предстательной железы, а также в эпителиальных опухолевых линиях. В линиях раковых клеток и резецированных тканях карцином были обнаружены мРНК константной области тяжелых (H) цепей IgG1, стерильный транскрипт Iγ-Cγ, H- и легкие (L) цепи IgG, V(D)J-рекомбинация генных сегментов H- и L-цепей, а также ферменты RAG1 (recombination-activating gene 1) и RAG2, необходимые для V(D)J-рекомбинации. Продуцируемый раковыми клетками IgG может быть вовлечен в инвазию и метастазирование этих клеток через взаимодействие с E-кадгерином, а также с белком-1, ассоциированным с метастазированием (MTA1). Опухолевые IgG играют важную роль в злокачественном прогрессировании, активируя тромбоциты путем взаимодействия с их рецепторами FcγRIIa и индуцируя выработку низких уровней активных форм кислорода. Уровень IgG в злокачественных новообразованиях положительно коррелирует с маркерами пролиферации, стадией развития, ростом и выживаемостью опухоли. Эти данные модернизируют представления о механизмах канцерогенеза и создают фундамент для поиска новых критериев диагностики и прогноза течения злокачественных новообразований, а также методов их таргетной терапии. Необходимы дальнейшие углубленные исследования феномена продукции Ig опухолевыми клетками для более эффективного практического использования накопленных в этой области знаний.

Ключевые слова: экспрессия иммуноглобулина, рак, иммуноглобулин нелимфоидного происхождения, иммуноглобулин опухолевого происхождения, канцерогенез, метастазирование.

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INTRODUCTION

Traditionally, only activated B-lymphocytes and plasma cells ale regarded as immunoglobulin (Ig) producers. However, according to some researchers, cells of non-lymphoid origin and non-lymphoid localization can also synthesize and secrete Ig. Expression of Ig genes was detected in malignant cells derived from epithelial tumors, such as breast carcinoma [1], colorectal cancer [2], prostate cancer [3], papillary thyroid cancer [4], lung cancer [5], and in cell lines of epithelial tumors, including cervical (HeLa S3), prostate (PC3), lung (A549), and liver cancer (BCL-7402) [6, 7]. In addition, Ig synthesis and secretion, as well as the expression of their genes, were found in non-malignant cells, including proliferating epitheliocytes [7], neurons [8], and some eye cells [9]. Ig produced and secreted by transformed cells belong to different isotypes (IgG, IgM, IgA and IgE) depending on the tumor type [10]. Ig detected in various human malignancies were found to enhance tumor growth and survival, and the levels of these molecules correlated with the markers of proliferation and the stage of

the neoplastic process [2, 11, 12]. Suppression of Ig production by small interfering RNA (siRNA), which blocks expression of the heavy chain gene of all Ig isotypes, resulted in inhibition of growth and proliferation of various cancer types *in vitro* and *in vivo* [13].

The aim of the study was to review the scientific literature on xpression of Ig by human epithelial tumor cells and potential significance of these molecules in carcinogenesis and metastasis.

MOLECULAR STRUCTURE AND GENETIC BASIS OF IMMUNOGLOBULIN DIVERSITY

Ig produced by classical antibody-producing cells (B-lymphocytes and plasma cells) represent a group of proteins with several structural similarities. The fine structure of Ig molecules was investigated using monospecific monoclonal antibodies produced by hybridomas obtained by fusion of activated B-lymphocytes with plasmacytoma cells. The basic structural unit (monomer) of Ig is composed of two identical light (L) chains with a molecular weight of 22.5 kDa and two identical heavy (H) chains with a molecular weight of 50–75 kDa, which are linked together by non-covalent and disulfide bonds. Both H and L chains contain amino-terminal variable (V) regions involved in antigen recognition and carboxy-terminal constant (C) regions. The C regions of the H chains mediate the effector functions of the antibody, which are not directly associated with antigen recognition. There are two types of L chains differing in the amino acid sequence of the C region: κ and λ. The complete Ig molecule is composed of one or more monomers. In humans, depending on the structural variant of the H chain C region (Cμ, Cδ, Cγ, Cα, and Cε), five classes, or isotypes, of Ig (IgM, IgD, IgG, IgA, and IgE) are distinguished, which differ in molecular weight, charge, amino acid sequence, and carbohydrate content.

The generation of Ig diversity is a result of somatic recombination of gene segments of the L and H chains located on different chromosomes. Each H and L polypeptide chain of Ig is encoded by several genetic elements that are physically separated in germline DNA. However, in B-lymphocytes and antibody-producing cells, these elements join and form a single active gene. The V domain of κ-type L chain is encoded by two different gene segments: Vκ (*Variable*) and Jκ (*Joining*). In germline DNA, these gene segments are far apart, but in the course of lymphocyte differentiation they join. When the combined Vκ and Jκ gene segments join the κ-chain C region gene, which is located relatively close to Jκ, a single active gene is formed. The combinatorial joining of Vκ and Jκ gene segments can provide a large number of L chain variants.

The H chain genes are characterized by more complex organization. Thus, the H chain V domain is formed due to the combinatorial joining of three types of germline gene segments: V_H, D_H (*Diversity*), and J_H. This provides even greater diversity of H chains as compared to L chains [14]. Ig gene rearrangement is mediated by coordinate activation of certain enzymes – V(D)J recombinases. Some of these are only found in developing lymphocytes. The rearrangement process is regulated by the lymphocyte-specific component of V(D)J recombinase that binds and cleaves DNA at specific sites, the so-called recombinant signal sequences. The enzymes required to initiate the DNA cleavage are a complex of two proteins encoded by the *RAG1* (recombination-activating gene 1) and *RAG2* genes. RAG1 is enzymatically active only in combination with RAG2. The level of RAG1 and RAG2 expression is influenced by interleukin-7 (IL-7), a cytokine secreted by stromal cells of the bone marrow [15, 16].

Two additional types of somatic changes in Ig genes contribute to Ig diversity. These are somatic hypermutation in the H and L chain V region genes [17] and changes in the H chain C region genes induced by cytokines during the T-dependent humoral immune response. Class, or isotype, switching from IgM or IgD to IgG, IgE or IgA results from the replacement of Cμ or Cδ exons by Cγ, Cε or Cα exons, respectively, without altering the antigenic specificity [18]. The activation-induced cytidine deaminase (AID) plays a key role in both processes. The exact mechanisms of this enzyme functioning are not fully understood; presumably, it may act as an RNA-editing enzyme [19, 20].

IMMUNOGLOBULIN EXPRESSION IN HUMAN EPITHELIAL TUMORS

The functioning of the humoral arm of the adaptive immune system in patients with various forms of neoplastic diseases, including epithelial tumors, has been the focus of research since the 1960s [21]. Since the 1970s, a number of studies have demon-

strated an increase in the blood serum IgG, IgA, and/or IgM levels in patients with non-hematopoietic neoplasia, including carcinomas of the cervix, breast, oral cavity, larynx, bronchi, kidney, and liver [22–25]. High concentrations of IgA in sa liva have also been detected in patients with laryngeal cancer [26]. For a long time, it was believed that Ig in tumor patients, as in healthy individuals, was produced only by B-lymphocytes and plasma cells. However, at the turn of the XX–XXI centuries, compelling evidence emerged suggesting that transformed epithelial cells may also produce Ig, which goes beyond the classical immunological paradigms.

In 1996, X. Qiu et al., using the immunohistochemistry analysis and Western blotting, first discovered IgG-like molecules in the breast and colon carcinoma cells and showed that these molecules are absent in the non-malignant epithelial cells of these organs [27].

In 1998, Y. Kimoto, using the nested reverse transcription polymerase chain reaction (nested RT-PCR) method, which allows for detection of extremely small amounts of mRNA, detected the transcripts of the H chain C region of IgM, IgD, IgG3, IgG1, IgE, and IgA in human carcinoma cell lines: SW116 (intestinal adenocarcinoma), Hep2 (laryngeal squamous cell carcinoma), MCF-7 and MDA-MB-231 (breast adenocarcinoma), and HC48 (pancreatic adenocarcinoma) [10].

Soon, expression of transcripts of the H chain C region and IgG production in epithelial tumor cells were confirmed by other researchers. Thus, using DNA microarrays, genomic analysis of the gene expression profile in 20 samples of primary human hepatocellular carcinomas revealed the H chain C region genes of IgG3 (*IGHG3*), IgA1 (*IGHA1*), and IgM (*IGHM*) [28].

In 2003, X. Qiu et al. used *in situ* hybridization, immunohistochemical analysis and PCR to demonstrate that human epithelial tumors, including breast, colon, liver, and lung carcinomas at the level of single cells obtained by laser microdissection, as well as cells of stabilized tumor lines produce cytoplasmic and secretory forms of IgG. IgG H chain transcripts and the corresponding protein were detected in the transformed cells. Using FACS analysis and Western blotting, authors detected IgG in long-term cultured human tumor cell lines: such as MCF-7 (breast cancer), HT-29, LOVO (colorectal cancer), BCL-7402 (liver cancer), A549 (lung cancer), CaOV3 (ovarian cancer), and HeLa S3 and HeLa MR (cervical cancer). IgG was also detected in the supernatant of HeLa S3 and HeLa MR cell cultures [11].

M. Li et al. evaluated Ig expression in 7 human epithelial carcinoma cell lines. Using the immunohistochemical staining, Western blotting, and solid phase enzyme immunoassay methods, IgA protein expression was detected in cell extracts and culture supernatants of all tested cell lines [29]. Expression of the IgG1 H chain C region gene (*IGHG1*) and IgG protein as well as RAG1 and RAG2 expression in epithelial tumor cell lines (breast, liver, cervix, prostate, nasopharyngeal, stomach, and colorectal cancer) were studied. The *IGHG1* transcripts and sterile Iγ-Cγ transcripts were detected by nested RT-PCR. The γ-type H chain and κ-type L chain proteins were identified by immunofluorescence and Western blotting. V(D)J recombination of the H and L chain gene segments and RAG1/RAG2 expression were also detected in the above cell lines [6].

In 2006, G. Babbage et al. performed gene analysis of the H chain V-region (V_H) in well-characterized breast cancer cell lines (BT 474, MDA-MB-231, MCF-7, SKBR3.T47D, and ZR-75-1) expressing the epithelial marker EpCAM (epithelial cell adhesion molecule) using nested RT-PCR. V_H gene transcripts were identified in 4 out of 6 cell lines. V_H gene expression was found in approximately 32% of single $EpCAM^+$ cells sorted from 3 tumor lines. In 5 of the 6 identified V_H genes, somatic mutations were detected without intraclonal variation, indicating cessation of mutational activity. V_H genes in the breast cancer cell lines were expressed as either pre- or post-switched transcripts, and in two cell lines, dual (both pre- and post-switched) transcripts were identified: IgG/IgA in SKBR3 and IgM/IgG in ZR75-1. However, at the protein level, the authors were unable to detect extra- and intracellular expression of Ig molecules in 4 selected cell lines using FACS analysis with monoclonal anti-IgG and -IgM antibodies. Analysis of RAG1 and RAG2 expression in each cell line showed the absence of any gene transcripts. When discussing the origin of rearranged V_H genes in tumor cells, the authors did not exclude the acquisition of these

genes as a result of the uptake of B-cell chromatin and its assimilation in the tumor cell genome. [30].

L chains of Ig expressed by cancer cells predominantly belong to the κ-type. Liu H.D. et al. in 2007 determined the expression of κ-chain genes in nasopharyngeal carcinoma cell lines by RT-PCR, Western blotting, and FACS. The expression of κ-chain C region mRNA was detected in abnormal cells of the cervical uterine epithelium in cervicitis and cervical intraepithelial neoplasia, as well as in invasive cervical carcinoma cells, and this expression was higher in dysplasia and carcinoma than in cervicitis [31, 32]. Expression of κ-chains was found in other tumors, such as breast, lung, liver and prostate cancer [6], colorectal carcinoma [33], and gastric cancer [34].

A number of studies were devoted to determining the molecular mechanisms of Ig expression in tumor cells. Both mRNA and proteins of RAG1 and RAG2, which are required for V(D)J recombination, were detected in Ig-positive tumor cell lines, including lung, colorectal, cervical [11], hepatic, prostate, gastric, breast, and nasopharyngeal carcinomas [6]. The expression of AID, which is required for class switching and somatic hypermutation, was detected by nested RT-PCR in 6 breast cancer cell lines [30], as well as in papillary thyroid cancer cells [4]. RAG1 and RAG2 mRNA as well as AID mRNA were detected in lung adenocarcinoma cells but not in cells of adjacent normal tissue or normal lung epithelial cell lines [5].

Importantly, AID transcripts were also detected in mammalian pluripotent tissues, including oocytes and primordial germ cells at a level comparable to AID expression in lymphoid tissues [35]. It was suggested that AID plays a role in epigenetic reprogramming and maintenance of the malignant phenotype. It is also possible that aberrant mutations and genomic instability are associated with high levels of AID expression [36].

B cell generation and Ig production are controlled by regulatory components such as receptor tyrosine kinase Flk2, IL-7 receptor (IL-7R), and transcription factors PU.1 (purine box factor 1), Ikaros, E2A (E box binding protein 2A), EBF (early B cell factor 1), and Pax5 (paired box protein 5) [37–39]. In *E2A*-/- or *EBF*-/- mice, B cell development stopped early in the absence of RAG expression and D_H-J_H rearrangement at the IgH locus. Ectopic expression of E2A and EBF1 together with RAG1 and RAG2 activated D_H-J_H rearrangement in non-lymphoid cells [40]. L. Geng et al., using nested RT-PCR, determined Pax5 expression in the human colon cancer cell line SW480 and EBF expression in several human epithelial neoplasia cell lines, including colon tumors (SW480 and LOVO), cervical cancer (HeLa), breast cancer (Bcap-37), and liver cancer (SMMC-7721) [33].

FUNCTIONAL ROLE OF TUMOR-DERIVED IMMUNOGLOBULINS IN CARCINOGENESIS AND POTENTIAL MECHANISMS OF THEIR ACTION

The functional role of IgG produced by epithelial tumor cells was analyzed in several studies, the results of which suggest that tumor-derived IgG enhances tumor growth and survival. In 2003, X. Qiu et al. showed that blockade of tumor-derived IgG by antisense oligodeoxynucleotides or antibodies to human IgG resulted in activation of programmed cell death and suppression of tumor cell growth *in vitro*. In addition, antibodies to human IgG suppressed the growth of the IgG-producing carcinoma cell line HeLa MR in immunodeficient nude mice [11].

In 2006, Y. Deng et al. determined the Ig expression in HT-29 cells (human colon cancer) and evaluated the effect of Ig on the biological activity of tumor cells. Transcripts of Ig H chain V regions (V_H CDR3) in HT-29 cells were detected by RT-PCR. Transfection of the antisense vector CDR3-pIRES 1 neo into HT-29 cells resulted in a significant decrease in Ig expression as well as in induction of apoptosis and inhibition of cell growth [41]. In human HeLa (cervical cancer) and CNE1 (nasopharyngeal carcinoma) cell lines, the blocking antibodies to α-type H chain (Igα) suppressed growth and reduced cell viability. In addition, Igα blockade led to a decrease in the proportion of HeLa cells that entered the S phase of the cell cycle after pre-synchronization in the G2/M phase [42].

The effects of IgG expression on growth and metastasis were studied in the tissues of squamous cell carcinoma and adenocarcinoma of the lung. The level of IgG expression in 86 lung cancer samples was found to be associated with the clinical stage of the tumor and its metastasis to lymph nodes.

Knockdown of IgG by siRNA resulted in decreased proliferation, migration, and adhesive capacity of cultured tumor cells. The relationship between the expression of IgG genes and the expression of metastasis-associated genes (CD44, E-cadherin, matrix metallopeptidase 9 (MMP9), MMP2, integrin-β1, and metastasis-associated protein MTA1) was evaluated by RT-PCR and Western blotting. Only MTA1 expression was found to be significantly reduced in lung cancer cell lines after inhibition of IgG expression. High MTA1 expression is known to be closely associated with cell invasion of various carcinomas and their metastasis to lymph nodes, as well as with progression of cancer symptoms [43, 44]. Suppression of MTA1 expression by siRNA in lung cancer cells inhibited their ability to migrate and adhere in cell cultures. Apparently, MTA1 is co-expressed with tumor-derived IgG, which may play a key role in the lung cancer metastasis through MTA1 regulation [5].

J. Wang et al. found that suppression of IgG mRNA and protein expression by siRNA in HeLa cervical cancer, Hep2 laryngeal carcinoma, and PC3 prostate cancer cell lines inhibited the growth and proliferative activity of tumor cells. Among 27 detected proteins, which interacted with IgG in HeLa cell culture, the following peptides were found to be closely related to cell growth and oxidative stress: RACK1 (receptor for activated C kinase 1), RAN (Ras-like guanosine triphosphatase), and PRDX1 (peroxiredoxin-1). Negative regulation of tumor-derived IgG was found to reduce the intracellular levels of reactive oxygen species (ROS) and increase to increase the overall cellular antioxidant activity. Several ROS scavengers, including catalase, dimethyl sulfoxide, N-acetylcysteine, and superoxide dismutase, inhibited the growth of IgG-deficient tumor cells through suppression of MARK/ERK (mitogen-activated protein kinase/extracellularly regulated kinase)-mediated signals [45]. Exogenous hydrogen peroxide at a low concentration enhanced the survival of these cells through an increase in the intracellular ROS levels [45, 46].

In 2013, P. Liang et al. showed that blockade of tumor IgG with human IgG antibodies or antisense oligonucleotides enhanced apoptosis and suppressed the growth of T24 and BIU-87 bladder cancer cell lines *in vitro* and the growth of tumor xenografts *in vivo*. In addition, inhibition of IgG expression in T24 cell line increased cell sensitivity to mitomycin C and activated caspase-3. Blockade of IgG expression is thought to induce tumor cell apoptosis through activation of the caspase-dependent pathway [47].

G. Lee et al. assessed the expression and functional role of tumor-derived IgG in OC-3-VGH ovarian cancer cells and in many other cancer cell lines from different human tissue origins by immunohistochemistry and immunofluorescence using RP215 monoclonal antibodies. RP215 specifically recognize tumor-associated CA215 antigen, which is expressed in secretory and membrane-bound forms in most cancer cells and consists mainly of tumor-derived IgG H chains. A unique glycosylated H chain epitope of tumor-derived IgG, which reacts with RP215, was characterized. CA215 was shown to be homologous to the H chain of human B cell-derived IgG1 with the molecular mass of 50–70 kDa with the exception of the high content of serine and threonine residues in the V region. A significant correlation of high tumor-derived IgG expression with low level of differentiation and late stage of cancer was revealed using RP215 antibodies [48, 49].

The same research group showed the expression of other proteins of the Ig superfamily in various cancer cell lines. Using MALDI-ToF MS (Matrix-Assisted Lazer Desorption / Ionization Time-of-Flight Mass Spectrometry) analysis, molecular homology of CA215 was revealed not only to H-chains of tumor IgG, but also to T-cell receptors (TCR) and Ig-like adhesion molecules. Using RT-PCR and cDNA sequencing, significant expression of the TCR-α and TCR-β genes, as well as the adhesion molecules CD47, CD54, CD58, and CD147, was found in the vast majority of cancer cell lines tested. In contrast, TCR co-receptors and co-stimulators, such as CD3, CD4, and CD8, were rarely expressed, which indicates the non-functional nature of TCR in tumor cells. These data were supported by the results of immunohistochemical staining and Western blotting of cancer cell lines, as well as cancer tissue samples. It was hypothesized that the expression of Ig superfamily proteins may be related to immune protection and proliferation of cancer cells during carcinogenesis and cancer progression [50].

Immunohistochemical analysis of tumor tissue samples taken from 100 patients with colorectal cancer made it possible to establish that tumor-de-

rived IgG, detected using RP215 antibodies, were expressed in cancer nests of tumor tissues, but not in stromal cells of colorectal tissues. It was found that high level of expression of tumor-derived IgG was a prognostically unfavorable factor. Expression of these IgG was also detected in 3 out of 5 colorectal cancer cell lines tested. Knockdown of tumor-derived IgG in SW480 cells suppressed their proliferation *in vitro*. Blockade of the tumor-derived IgG expression in SW480 cells prior to their subcutaneous injection into nude mice inhibited the growth of the implanted tumor *in vivo*. Direct interaction of IgG of tumor origin with E-cadherin and β-catenin was found. In normal cells, these adhesion molecules form a single complex located in the adherens junctions on the cell membrane. As a result of the knockdown of tumor-derived IgG, the expression of E-cadherin at the adherens junctions increased, while the expression of c-Myc oncogene decreased. The authors speculated that tumor-derived IgG might cause dissociation of E-cadherin from the complex with β-catenin and activate β-catenin / c-Myc-mediated signaling by increasing nuclear translocation of β-catenin, thereby promoting invasion and metastasis [51].

In 2015, Q. Liao et al., using RP215 antibodies, showed that cancer cells with high level of IgG expression were characterized by increased ability to migrate, invade, and metastasize *in vitro* and *in vivo [52].* IgG knockdown in cancer cell lines and in breast cancer resulted in significant inhibition of tumor cell proliferation, migration, and invasion, as well as in induction and enhancement of tumor cell apoptosis [52, 53].

Recently, it has been found that IgG of tumor origin activated platelets by direct interaction with their FcγRIIa receptors [54], which was reflected by increased secretion of dense granules by platelets [55]. It is known that platelets can regulate tumor growth, angiogenesis, and metastasis [56–58], which is associated with the functions of surface receptors and secreted products, such as thromboxane, platelet growth factor [59], and vascular endothelial growth factor [60]. Tumor-related thrombotic complications are one of the leading causes of death in cancer patients. Patients with thrombosis are more likely to have distant metastases, and their one-year survival rate is lower than that of patients without thrombotic complications [61–63].

CONCLUSION

This review presents in chronological order the results of key studies on Ig expression by epithelial tumor cells and the significance of these molecules in carcinogenesis and metastasis. Since the late 1990s, there has been rapid progress in this scientific field from random ("paradoxical") findings of extra-lymphoid Ig production to detailed immunological, genetic, and clinical characteristics of this scientific phenomenon. This information, together with the data on Ig production by normal proliferating epithelial cells, central neurons, and eye cells, substantially modernizes the traditional concepts, according to which V(D)J recombination and Ig production are characteristic only of B-lymphocytes and plasma cells, which requires revision of the classical immunological paradigms in the field of humoral immune response.

The expression of Ig, mainly IgG, of unidentified specificity in epithelial tumors and cancer cell lines of different organ origin is worth noting. Tumor-derived IgG has been shown to be structurally and functionally distinct from the antigen-specific Ig (antibodies) produced by B cells and to be involved in cancer cell growth and survival. Using different methodological approaches, independent research groups consistently excluded factors that could influence the final study results in order to confirm the tumor origin of Ig. Today, there is no doubt about the universal (or near-universal) ability of epithelial tumor cells to produce Ig.

The search for new molecular markers of tumorigenesis is an important and promising direction in immunodiagnostics and immunotherapy of malignant neoplasms [64]. The expression of Ig, mainly IgG, by cancer cells closely correlates with the clinical stage, the degree of pathological changes in tumor, and metastasis to lymph nodes. A positive correlation between IgG expression and clinical parameters of the tumor process suggests the possibility of determining the expression of tumor-derived IgG in oncological practice for diagnostic and prognostic purposes.

The molecular mechanisms and the biological and clinical significance of Ig production by non-lymphoid cells, especially cancer cells, require further in-depth investigation. It remains to be established whether Ig of non-lymphoid origin have

the same functions as Ig produced by B cells or plasma cells. The similarities and / or differences in the mechanisms of Ig production by lymphoid and cancer cells should be elucidated. The question remains whether Ig expression in tumor cells is the cause or the result of cell transformation. It is useful to clarify whether tumor-derived Ig can be used as a therapeutic target in neoplastic diseases. It is likely that the answers to these questions could form the basis for the development of methods for the selective blockade of IgG produced by cancer cells in the therapy of malignant neoplasms.

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