INTERACTION BETWEEN TUMOR AND IMMUNE SYSTEM: THE ROLE OF TUMOR CELL BIOLOGY

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In present work the role of tumor cell biology upon different conditions of their interaction with the cells of immune system is discussed. The presented data show that it tumor cell biology that in many cases determines tumor antigen recognition and realization of cytotoxic action of killer cells. Here also we discuss own data obtained with the use of experimental tumor models (transplantable MC-rhabdomyosarcoma, B16 melanoma) and human tumors (soft tissue sarcoma, melanoma, breast cancer, ovarian cancer, cervical cancer). It was demonstrated that various tumors have different sensitivity to antitumor action of activated (LAK) and non-activated lymphocytes. Recent studies on the role of tumor cells in expansion and activity of different suppressor cells (MDSC, Treg, Th17, M-2 macrophages, etc.) are overviewed. The role of organ-specificity and interaction of the components of microenvironment (cells of immune system and stroma, tumor cells, endothelial cells, extracellular matrix) are discussed in details. Along with the presentation of modern views on some patterns that characterize the development of drug resistance of different tumors and capabilities of immune system cells to participate in lysis of resistant tumor cells, the authors present their own data illustrating that resistant tumor cells reveal increased sensitivity to LAK. An analysis of the involvement of a number of molecules, lymphocytes, and tumor cells in the phenomenon of elevated sensitivity to LAK action allowed to conclude that tumor cells reveal high sensitivity at the background of decreased E-cadherin expression and increased CD40 expression.

Key Words: tumor cell biology, recognition, immunosuppression, resistance, LAK, E-cadherin, CD40.

At the end of 90th, a significant number of data have been accumulated and have created an important field in oncology — tumor cell biology. This area of research allowed to widen the knowledge about the complex interactions between tumor and organism. The role of biological patterns of tumor cells is especially prominent upon their interaction with the cells of immune system. At present time it is considered that the result of interaction between immune system cells and tumor cells is equally dependent on the functional state of immune system cells, and on biological patterns of tumor cells.

If one analyze different aspects of such interaction, it becomes clear that biological properties of tumor are reflected in: 1) recognition of tumor antigens; 2) character of immunologic response (growth inhibition or stimulation, tolerance); 3) expression of antitumor action of killer cells; 4) formation of immunosuppression; 5) influence of tumor cell patterns on formation of microenvironment; 6) development of resistance to killer cell action and drug resistance; 7) efficacy of immunotherapy etc.

Understanding the role of tumor cell biology for its interaction with the cells of antitumor defense allows to approach to the answers on numerous principal questions concerning fundamental aspects of tumor immunology and clinical immunotherapy, namely: 1) Why tumor cells escape from immunological control? 2) Why there is no immunological response without visible disturbance in immune system cells (in particular antigen-recognizing and killer cells)? 3) How can tumor cell suppress immunological response? 4) What is the role of tumor in activation of cells with suppressor activity? 5) How biological patterns of tumor cell are reflected in formation of microenvironment? 6) Why immunotherapy is presently low-effective? etc.

RECOGNITION OF TUMOR ANTIGENS

It is well known that recognition of antigens, in particular, tumor ones, is a complex integral multifactor process that depends on expression and functional state of numerous surface and intracellular structures of tumor cells and lymphocytes. This is related, firstly, to expression by tumor cells of adhesive molecules, I and II classes MHC antigens, expression and functional activity of transport proteins (TAP-1, TAP-2), and also PSF1, PSF2-peptide supply factors, LMP (large multifunctional protease) and its subunits — LMP-1, LMP-2A, LMP-2B, LMP-7, LMP-10, β2-microglobulin, MECL-1, PA-28α, PA-28β proteins, tapostin etc.

One could present many examples of the role of tumor cell biological patterns for an efficacy of antigen recognition and processing. Among these, the characteristics of proteins involved in presentation process should be mentioned. If taking into consideration just TAP and LMP, it’s evident that the rate of abnormal
expression of these proteins is different in different types of tumors. Defective TAP expression is the mostly frequent in melanoma (that’s why MHC I class antigen expression is practically absent in melanoma cells) and renal cancer. In contrary, in lung cancer cells and intestinal cancer TAP expression is practically unaltered, while in nasopharyngeal cells lines decreased TAP expression doesn’t lead to altered HLA-A2 expression [1].

Altered presentation process may be related also to the changes of expression of different LMP proteins — LMP-1, LMP-2, LMP-7, LMP-10 etc. that occupy the central place in antigen presentation process on antigen-presenting cells as well as on tumor cells. As a rule, the decreased activity of these proteins is observed, and such decrease is interrelated with tumor cell patterns: for example, gangliosides produced by prostate cancer cells decrease LMP-10 expression in dendritic cells thus altering presentation process [2]. In some cases, in particular in esophageal cancer, combined change of expression of proteins involved in presentation (simultaneous decrease of LMP-2 and TAP-1 expression levels) could be registered [3]. Presently it is evident that recognition process is extremely important and should be considered and controlled during cancer immunotherapy as the first stage of interaction between tumor and immune system. Knowledge on tumor cell patterns is required for prognosis of immunologic response on therapy due to the possibility of its opposite action.

SENSITIVITY TO THE ACTION OF KILLER CELLS

The main criterion of recognition effectiveness and respectively of antitumor action of killer cells is the damage of target cells. The degree of tumor cell sensitivity to the action of killer cells differs in tumors of various histogenesis, localization and the stage of tumor progression, as well between the cells of the same tumor. Along with this, different sensitivity exists as well toward special populations of killer cells — CTL, NK, NKT, macrophages, neutrophils, etc. In some cases the maximal antitumor effect is achieved upon the action of CTL, in some cases — of NK and NKT, in some cases there is a prevalence of neutrophil activity (especially at early stages of tumor process), sometimes — an efficacy is achieved upon combined action of different cells, and at last, killer cells, eosinophils or basophils may be involved, but their action is poorly studied yet [1].

Unfortunately, recognition not always results in destruction of tumor cells. The degree of sensitivity of tumors and cell clones from the same tumor could differ and depends on a number of conditions. This is evidenced by the results of studies of solid tumors, among which melanoma is the most frequently studied object. First of all, it is related to the sensitivity of cells of primary and metastatic melanoma to cytotoxic action of CTL, NK, NKT etc. It is known that NK cytotoxicity strongly depends on expression of different activatory receptors, among which the most important are NKG2D, NCR (NKp46, NKp30, NKp44), DNAM-1 (co-stimulatory molecule). The cells may differ by the expression levels and density of these receptors [4–7]. However, the expression of these receptors, their surface density and functional activity could not guarantee tumor cell lysis. Necessary condition for lysis is the expression of recep- tors’ ligands by tumor cells. Ligands for NKG2D are MIC (MICA, MICB) associated with nonclassic I class MHC, and ULBPs (ULBP1, ULBP2, ULBP3, ULBP4) — the members of large protein family related to cytomegalovirus UL16. The members of ULBP family may serve as the ligands for NCR, while CD155 (poliovirus receptor PVR) and N-ectin2 (CD112) are ligands for DNAМ. — From two DNAM-1 ligands CD155 is frequently expressed in melanoma cells, while CD112 — rarely [4–7]. The recent data have shown that DNAM-1 plays a central role in control of recognition of metastasing cells, and is responsible for the response to immunotherapy with the use of IL-2, IL-12 and IL-22 [5]. Such role of DNAM-1 is determined by its participation in realization of activating signals received from tumor cells. The role of DNAM-1 and CD155 interaction for lysis of metastasing cells is determined by the activation of perforin system.

Receptors of killer cells, for example, NK, often vary by recognition of different ligands, while tumor cells significantly vary by ligand expression [6, 7]. For example, high expression level of ligands to activatory receptors and low level of ligands to inhibitory receptors is typical for cervical carcinoma cells [8]. Melanoma cells are heterogeneous by MICA and ULBP2 expression even in metastases. Among soluble forms of these ligands, MICA is detected much more rarely than ULBP2. On the cells of different carcinoma the most frequently MICA and ULBP1 are expressed; highly differentiated tumors of invasive breast carcinoma are characterized by high MICA expression [9, 10].

Variability of killer receptors on lymphocytes and their ligands on tumor cells partially explain the different sen- sitivity of tumor cells to the action of killer cells, which is supported by a numerous data. For example, the study of different glioma cell lines that express ULBP2 and ULBP3, or ULBP1 and ULBP4, has shown that in first case the cells were highly sensitive to NK-mediated lysis, and in the other — were low sensitive [11].

Apart from expression patterns of mentioned recep- tors and their ligands, the lysis may be hindered by soluble forms of these ligands produced by tumor cell — sULBP2 and sMICA, as well as soluble form of sNKG2D receptor. At last, inhibitors of mentioned ligands also may contribute to the disruption of tumor cell lysis, in particular matrix metalloproteinases expressed by tumor cell [12].

Another important component of cell lytic process is presented by adhesion molecules grouped in five large families. In 1990 it was shown that cells highly sensitive to CTL could be characterized by ICAM-positive phenotype. Presently it is known that ICAM-1 plays an important role in realization of cytotoxicity: the study of cells of primary and metastatic melanoma has revealed that primary melanoma cells express ICAM-1 and demonstrate an expressed sensitivity to CTL, while
cells of metastases with low sensitivity to CTL do not express the molecule. In melanoma metastases inhibitor of granzym B has been found [13].

The cells of different tumors differ not only by the level of ICAM-1 expression, but also by intracellular signals induced via interaction of this molecule with its ligand. Such interaction in breast cancer cells results in activation of transcription factor Fos related antigen-2 that is accompanied by elevated invasion and metastasis [14], while in melanoma analogous interaction leads to activation of NF-κB with the involvement of TNFα [15].

Along with intracellular ICAM-1 molecule and its soluble form, also membrane-bound mICAM-1 has been described. The role of mICAM-1 is yet poorly understood but it has been shown that it may interact with lymphocytes decreasing their adhesion capacity, and could be found only in portion of tumor cells. Comparative study of mICAM-1 in prostate cancer cells and breast cancer cells demonstrated that this molecule was present in prostate cancer cells, but was absent in breast cancer cells [16].

CD40 glycoprotein from TNF receptor family could be ascribed to multifunctional molecules involved in cytotoxicity process. CD40 molecule plays a central role in cell proliferation, activity and survival [17]. An interest to this molecule and its involvement in malignant growth is based on a number of important facts. Many solid tumors (melanoma, renal, bladder, breast cancers etc) express CD40 receptor, some express CD40 ligand (CD40L), and in some cases simultaneous expression of CD40 and CD40L may be detected [17]. CD40/CD40L-interaction may cause oppositely directed effects — tumor cell death and increased tumor growth with involvement of different mechanisms. CD40 expression may be associated with drug resistance via caspase-dependent or caspase-independent pathways [17]. CD40 expansion and its activation is often accompanied by expression of co-stimulatory and adhesion molecules, Fas-antigen etc.CD40 may interact with myeloid-derived suppressor cells (MDSC) and regulatory T cells (Treg) [18]. Nowadays it became possible to explain ambiguosity of influence of CD40/CD40L interaction of tumor growth. It has been shown that low ligation level (as a rule, with involvement of soluble CD40L) increases survival and proliferation, while high ligation level (mCD40L) results in apoptosis. The mentioned studies were performed on bladder carcinoma cells and allowed to conclude that the result of CD40/CD40L interaction depends on the balance between the signals inducing survival and apoptosis [19].

For characterization of tumor cell sensitivity of various human and animal tumors to antitumor action of autologous lymphocytes, we have studied interaction of tumor cells (soft tissue sarcoma, cervical cancer, ovarian cancer, breast cancer, melanoma, models of MC-rhabdomyosarcoma and B16 melanoma) with lymphocytes in diffusion chambers. Tumor cell sensitivity has been studied toward activated and non-activated lymphocytes. It has been shown that sensitivity of different tumors to the action of autologous non-activated lymphocytes varies. The most expressed antitumor activity has been registered for lymphocytes of patients with soft tissue sarcoma, and the lowest one — for lymphocytes of patients with cervical cancer. Melanoma cells, ovarian and breast cancer cells revealed similar sensitivity to the action of lymphocytes. We have noted an expressed heterogeneity of sensitivity to the action of autologous lymphocytes of tumor cells of common genesis and histogenesis (skin melanoma, soft tissue sarcoma). During the study of tumor growth dynamics on different models it has been detected that at the stage of tumor growth activation, lymphocytes of animals bearing MC-rhabdomyosarcoma inhibited tumor growth, and with melanoma — stimulated it.

To find out with what molecules expressed in lymphocytes and tumor cells are involved in regulation of antitumor activity, we have studied the expression of CD25, ICAM-1, CD56, CD11b, CD71, CD40, p53, and marker of proliferating cells IPO-38. As we have shown, an expressed antitumor activity of lymphocytes of patients with soft tissue sarcoma was associated with ICAM-1 expression by tumor cells, and CD11b, CD25 on lymphocytes. For melanoma, no statistically significant results were obtained.

Differences in antitumor activity of LAK activated by IL-2 were found to be more expressed in different human tumors and animal models, in particular: 1) antitumor activity toward soft tissue tumor cells was even higher; 2) activity of lymphocytes of cervical cancer patients was sharply elevated; 3) activity toward ovarian and breast cancer cells was significantly elevated; 4) IL-2 activation neutralized stimulation of melanoma growth and significantly potentiated an antitumor action of LAK toward MC-rhabdomyosarcoma cells. Overall, different human and animal tumor cells demonstrated various sensitivity to the action of autologous lymphocytes, activation of which in some cases drastically increased their antitumor action, in some cases — markedly increased, and in some cases — neutralized the negative effect of non-activated lymphocytes.

Taking into account the role of CD40 expression in tumor cells for antitumor activity of lymphocytes, we have studied CD40 expression in breast cancer cells (duct carcinoma and different benign tumors), and have shown that benign and malignant breast tumor differed by CD40 expression, which was significantly higher in malignant tumor cells. It was found that an expressed antitumor activity of peripheral blood lymphocytes was in many cases associated with high expression level of CD40 receptor by malignant tumor cells.

To prove the role of CD40 expression in tumor cells for lymphocyte activity, we performed a study with blocking of CD40 on tumor cells by recombinant CD40L protein. It resulted in the significant decrease of the activity of regional lymph node lymphocytes, and at much lower degree — peripheral blood lymphocytes of the patients.

**IMMUNOSUPPRESSION**

One of the most important achievements of modern immunology is identification of the different types
of cells with suppressor activity. The relation exists between the expansion of various cell types with suppressor activity and biological patterns of tumor cells. It is grounded on the fact that tumor cells significantly differ by the level of production of various substances—inducers of cells with suppressor activity. Inducers of cells with suppressor activity account some tumor antigens, arginase-1, prostaglandins, iNOS, NO, ROS, such cytokines as SCF, M-CSF, GM-CSF, VEGF, IL-6, various chemokines and other cytokines [20]. Presently few cell populations and subpopulations with suppressor activity are identified: MDSC, CD4+CD25+FOXP3+ (Treg), CD69+CD4+CD25-FOXP3+CD122+, suppressor CD8 T-lymphocytes that express CD28, CD29, CD57, CD94 and at low level different activation markers, macrophages-2 (M-2); at certain conditions suppressor action can be caused by Th17, mast cells, basophils, eosinophils, etc. [1]. The majority of mentioned populations and subpopulations of suppressor cells are heterogeneous and are presented by different cell clones. Presently the most studied suppressor cells are MDSC and Treg that possess wide spectrum of immunosuppressive influence toward NK, NKT, effector CD4- and CD8-lymphocytes, maturation of dendritic cells, and also are able to promote inflammation, angiogenesis, damage of epithelial barrier thus enhancing metastasis, etc. [20]. Inflammation creates a favorable background for expansion of all suppressor cells, and many pro-inflammatory cytokines promote their accumulation. Activity of suppressor cells becomes essentially expressed at the conditions of tumor microenvironment, and the polarization of macrophages of microenvironment to M-2 illustrates such statement [21].

MDSC could be detected upon the development of many human and animal tumors in peripheral blood, spleen and area of tumor localization. There is a hypothesis that in humans MDSC of various localization possess similar CD11b+CD33 CD34 CD14 HLA-DR- phenotype [22]. At present it has been estimated that in some tumor cases other MDSC subtypes are formed. In particular, in melanoma and hepatocarcinoma patients, CD14+ and HLA-DRlow subtype has been found while in enteric carcinoma MDSC possess characteristics similar to these of macrophages [22]. Intracranial administration of glioma cells of TL line to rats resulted in formation of MDSC that express such markers as His48 and CD11b. These cells express arginase-1, iNOS, TGFβ1 etc., but still NO is considered as a primary mechanism of suppression [23].

Recently, in many tumors (liver and lung cancers, melanoma) subpopulations of suppressors that do not express CD25 and FOXP3 were identified. Their number increases along with tumor progression, and they differ from other CD4+CD25+ suppressor cells by expression of CD122 and membrane bound TGFβ1, as well as an absence of IL-10 production [24].

Suppressor cells may reveal independent suppressor activity, or act synergistically as it has been shown for MDSC and Treg. It is known that the development of tolerance toward special tumor antigens (some tumor cells differ by the content of such antigens) creates a significant barrier for lysis by killer cells and for efficacy of some types of immunotherapy. That’s why it is of interest that the development of tolerance is associated with accumulation of MDSC and Treg, while the presence of MDSC favors to Treg generation. Moreover, expression of CD40 by MDSC that further interact with CD40L of T-lymphocytes is required for Treg accumulation [18]. These data revealed new properties of MDSC and demonstrated that CD40/CD40L blocking may serve as a therapeutic approach. However, it should be considered that such blocking may have negative consequences as well.

Different suppressor cells differ by an ability to react on the action of various inducers of their expansion. For example, MDSC express receptors to PGE-2 that is an inducer of some suppressor cells. However, different tumors differ by production of this mediator. For example, murine mammary gland carcinoma (4T1) is characterized by high accumulation of PGE2 and MDSC in parallel with accumulation of pro-inflammatory cytokine IL-1α [25]. In some tumors Fas/FasL-interaction may mediate not pro-apoptotic functions, but promote the proliferation, and such fact has been noted in PGE2-dependent 3LL lung cancer. It has been shown that MDSC accumulation occurs with the involvement of PGE2, inflammation development, progression and tumor escape from immunological control [26].

Similarly to other cells, for manifestation of suppressor activity of Th17-lymphocytes inflammation is favorable, too. These cells are accumulated in melanoma, enteric cancer, and breast cancer [27]. At certain conditions Th17-lymphocytes may also reveal synergistic action with other suppressors, for example, Treg-lymphocytes. In many tumors a significant amount of infiltrating lymphocytes is represented by Th17 in combination with increased IL-17 level. High level of Th17 infiltration is observed in hepatocellular carcinoma, while infiltration density by lymphocytes correlates with blood vessel density and duration of remission period [28]. Taking into account these facts, the authors concluded that Th17-cell accumulation and increased IL-17 production may serve as a prognostic criteria for hepatocellular carcinoma, and Th17-lymphocytes — as a target for therapy [28].

Organ specificity affects manifestations of suppressor activity of Treg too, and this has been observed in glioma and skin cancer [29, 30].

All mentioned above suppressor cells are characterized by unspecific influence on different effector cells. However, wide spectrum of their inhibiting effects may be reflected also in inhibition of cells involved in formation of antitumor immunity. First of all, it is related to expansion of tumor-specific cytotoxic T-lymphocytes. A possibility of different suppressor cells induction and their activity level at large extent depend on biological properties of tumor cells and their organ specificity.
TUMOR MICROENVIRONMENT

Biological properties of tumor cells manifest itself in tumor microenvironment, and the patterns of its formation depends on the following main factors: 1) organ specificity differing between organs and tissues (determines composition of stromal components and vascularization); 2) functional activity of immune cells, stroma; 3) extracellular matrix; 4) tumor cell patterns; 5) character of interaction between the components of microenvironment; 6) complex system of regulation with involvement of different cytokines and other biologically active molecules produced by all components of microenvironment [31]. Active interaction between all components of tumor microenvironment (fibroblasts, myofibres, endothelial cells and immune system, extracellular matrix) and tumor cells occurs in microenvironment of all solid tumors and determines at large extent the phenotypic patterns of tumor cells, their ability to metastasis, invasion, neovascularization as well as the properties of other cellular components of microenvironment (phenotype, cytokine secretion).

Metabolic and pathophysiologic patterns of microenvironment are also important. This field is also actively studied, and presently many transcription factors were described, which regulate different functions of cells in microenvironment, hypoxia and the level of production of hypoxia induced factors (HIFs), patterns of oxygen transport and metabolism of iron, glycolysis, etc. [32]. However, it remains unclear what is the relation between metabolism, pathomorphologic patterns and components of microenvironment.

At present time the cells of stromal microenvironment, their interactions with tumor cells and immune system are actively studied. The most popular object of such studies are fibroblasts that at normal state restore homeostasis, but upon tumor development and influence of different factors could differentiate into myofibroblasts, express MMPs, participate in induction of immunosuppression, promote extracellular matrix remodeling and acquire new phenotypic patterns [33]. There are no doubts that stromal cells are able to affect tumors bipolarily, because they may participate in tumor regression or promote tumor growth. The latest statement is supported by the data that melanoma fibroblasts may suppress NK cytotoxicity, cytokine production by these cells, and inhibit their activatory receptors — NKp44, Nkp30, DNAM-1 [34].

As it has been shown, fibroblasts may be involved in activation of resting tumor cells, deposition of type I collagen (Col-I) and development of fibrosis in microenvironment of melanoma metastases that promote their proliferation [35]. This is based on biochemical processes that lead to reorganization of cell cytoskeleton with active participation of β1-integrin and Col-I. At the microenvironment, favorable conditions for fibroblast activation are generated because tumor cells produce different soluble factors, in particular VEGF, TGFβ, PDGF, HGF that locally activate fibroblasts modifying their phenotype and functions. That has been observed in breast cancer cell when co-cultivation of MDA-MB-23 cells and fibroblasts elevates aerobic glycolysis that is used by tumor cells for its own growth [36].

Of interest is also the study of endothelial cells that determines vascularization intensity, capillary system, the state of vessel wall etc. — factors that at large extent depend on organ specificity. Endothelial cells of vessels actively participate in the interaction with stromal tumor cells, immune system, extracellular matrix, and this process is accompanied by secretion of various biologically active compounds, in particular, angiogenic factors. Developing hypoxia promotes SDF-1 secretion by epithelial cells increasing their adhesion to all cell types.

An influence of organ specificity on microenvironment patterns is reflected at the level of tumor stem cell. For example, stem cells isolated from glioma by many parameters do not differ from normal stem cells of nervous tissue — the property typical for brain tumor cells [37]. Glioma cells express molecules responsible for their migration and invasion, in particular PAR-2 — protease activated receptor-2 [38]. During glioblastoma growth normal monocytes may differentiate to MDS-like phenotype. This has been detected during the study of glioma cells from patients and in glioblastoma cell lines cultured with normal monocytes. Such monocytes produce IL-10, TGFβ, B7-H1, have decreased ability to phagocytosis and elevate apoptosis of target cells [39]. Possibly, such phenomenon could be explained by the patterns of local immunity of the brain.

The role of extracellular matrix is very important. It is composed from different proteins — MMPs, lyso-somal enzymes, deoxyribonuclease, elastase, etc. Dependent on conditions and organ specificity, protein composition of extracellular matrix may be altered because of active interaction of these proteins with all cells of microenvironment [31, 40].

At the conditions of microenvironment, there could be also alterations at genetic and epigenetic levels found even between the cells of the same tumor. At the background of genetic and epigenetic changes, metastatic potential of tumor cells is formed [29, 30]. Presently it is known that epigenetic changes are related to altered expression of the enzyme that methylates cysteine residues CpGs, and is involved in the development of malignant tumors [41].

So, microenvironment creates the conditions for altered interaction between the cells of microenvironment and extracellular matrix. That’s why it is accepted that invasion and metastasis are the results of altered cell-to-cell interactions as well interactions between separate cells and MMPs [14].

DRUG RESISTANCE

Among the most serious problems of modern oncology tumor drug resistance should be mentioned. This problem has been studied in plenty of researches, many molecular mechanisms have been revealed, and the role of genetic and epigenetic disturbance has been shown [42]. Drug resistance is determined by heterogeneous mechanisms that in part are mediated by biological
patterns of tumor cells. In particular, there are revealed notable differences in expression of proteins involved in the development of drug resistance. The majority of such proteins are related to ABC family (ATP-binding cassette), that includes MDR, P-gp, BCRP etc., but also some proteins, for example, lung resistance-related protein (LRP), that are not a members of this family. Comparative evaluation of expression of mentioned proteins by tumors evidences on their varied expression levels in different tumors. For example, melanoma, pancreatic carcinoma, rhabdomyosarcoma etc., possess high expression level of these proteins. However, some tumors or tumor cell lines of similar genesis may vary by expression rate of these proteins or their combinations. For example, in neurosarcoma MRP-1 was expressed in all primary tumors, P-gp and BCRP were expressed much more rarely, while in rhabdomyosarcoma — MDR-proteins were expressed in different combinations in the majority of cases. These data allowed concluding that parallel expression of different MDR-proteins may be caused by simultaneous involvement of different mechanisms of drug resistance formation that lead to decreased survival [43].

It is of special interest that mentioned above proteins are not only drug resistance markers, but are expressed also by many cells of immune system, participate in regulation of immunologic response, play role in differentiation, maturation and migration of these cells, enhance antigen-recognizing potency of dendritic cells [44]. Moreover, mentioned proteins may be recognized by immune system cells. This allows explaining an elevated sensitivity of some breast cancer cell lines to LAK action by P-gp expression [45].

The expression of tumor-associated antigens may cause cell lysis of resistant tumors. Resistant cells of Hodgkin’s lymphoma and primary tumors express MAGE A4, SSX2, survivin, and NY-ESO-1, that are recognized and lysed by cytotoxic T lymphocytes [46].

There is one aspect of this question — upon the influence of many抗癌 drugs some resistant tumors acquire elevated sensitivity to the action of killer cells. This is supported by the data showing an elevation of tumor sensitivity to NK-induced apoptosis, and many other reports. However, the positive effect of drugs on tumor cell sensitivity to NK action could be associated with their resistance to the action of killers from other population — cytotoxic T lymphocytes [47].

The studies performed by us with the use of cells from different tumors (experimental and clinical observations), resistant to different drugs, have shown the following. First, tumor cells (models of transplantable MC-rhabdomyosarcoma and B16 melanoma), resistant to doxorubicin reveal elevated sensitivity to LAK compared with sensitive tumor cells. Second, elevated sensitivity to LAK action has been revealed not only by resistant tumors of animals, but also by resistant human tumors. Third, elevated sensitivity to LAK action could be increased by pretreatment of resistant tumor cells by low doses of drugs [48, 49]. Forth, upon study of expression of E-cadherin, CD40, IPO-38, p53, pan-cytokeratin, CD54, CD11b, CD25, receptors of lectins (soybean, coral bean, lentil) by resistant tumor cells and lymphocytes () it has been shown that an expressed antitumor action of LAK is associated with high expression levels of CD40, p53, IPO-38, and decreased expression of E-cadherin in tumor cells, and elevated expression of CD25, CD54, receptors of soybean, and unaltered CD40 expression in lymphocytes. Combination of pronounced sensitivity to LAK action with decreased E-cadherin expression could be explained by the fact that decreased E-cadherin expression leads to distorted signaling with involvement of some transcription factors (Wnt, PKD-1, Int-2 etc.), accumulation of β-catenin in nucleus, activation of transcription factors NF-κB, AP-1 and others, with the following proliferation of tumor cells that makes them more sensitive to LAK action and leads to lysis [50, 51].

So, concluding this part, it is worth mentioning that the study of drug resistance has determined the creation of new field of research — interplay between immune system and drug resistant tumor cells.

IMMUNOTHERAPY

The presented facts allow concluding that an efficacy of different types of immunotherapy strictly depends on tumor cell biology, and its failure — on insufficient knowledge of these patterns in each particular case. However, this fact points on necessity of further studies in this field creating the basis for progress of oncomunology and development of new immunotherapeutical approaches. Knowledge on tumor cell biology explains why efficacy of immunotherapy is yet unsatisfactory: during tumor growth its antigenic composition, phenotype, character of interaction with stromal cells and immune system change steadily, and different stages of tumor growth are reflected in biological patterns of tumor cell. At all stages of tumor growth tumor cell realizes its «strategy» — the term introduced by H. Salih. That’s why to overcome these problems, it’s necessary to combine all required knowledge with maximal individualization of immunotherapeutical approaches.

CONCLUSION

Tumor cell biology includes numerous characteristics: antigenic composition and ability to induce different forms of immunologic response, phenotype, synthesis and production of cytokines and other biologically active compounds, ability to autocrine growth regulation, tumorigenecity, induction of suppressor cell expansion, invasiveness, metabolic potential, etc. In reality in each particular case it iss a difficult and not always feasible task to consider all mentioned above characteristics as well as other possible ones. Along with this it is evident that tumor cell “strategy” realized via its interrelation with the cells of immune system could not be overcome without considering special biological patterns of tumor cells, especially their ability to stimulate growth, induce the development of tolerance, and activation of suppressor cells. It seems to be true that immunotherapy should be based only at
mentioned fundamental approach, in particular, such promising types of therapy as vaccination and adoptive transfer of activated cells of immune system. Quick development of modern oncoimmunology allows believing that from complex parameters that reflect biological patterns of tumor cells, the properties that will guarantee the realization of any type of therapy will be selected — to help but to do no harm.

REFERENCES


